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TETANUS TOXOID IMMUNIZATION IN THE UNITED STATES NAVY *

By COMMANDER W. W. HALL, F.A.C.P., *Medical Corps, U. S. Navy*

THE purpose of this paper is to summarize the work on tetanus immunization done in the U. S. Navy since 1934, some of which has previously been reported,[1, 2] and to present a few thoughts concerning the value to the military services of active immunization against tetanus.

The development of toxoid immunization against tetanus is not entirely new. As long ago as 1926 Ramón [3] reported satisfactory immunization of humans using formol toxoid or anatoxin. Work on this subject was confined largely to France for the next few years. Then, on this continent from 1932 to 1936, various papers appeared, reporting on the immunization of animals as well as human beings. Papers were published by Lincoln and Greenwald,[4] Bergey and Etris,[5] Sneath,[6] Sneath and Kerslake,[7] and Hall.[1]

In the last three or four years, as active immunization with tetanus toxoid has been more widely used, the literature upon this subject, both here and in Europe, has grown rapidly.

Toxoid immunization develops active immunity. Active immunization is nature's method of protection. All naturally developed immunity to infectious disease, as well as immunity developed by vaccination, is active immunity. Active immunity is in general persisting immunity. Passive immunity on the other hand, although it may be highly effective under properly controlled conditions, is merely stop-gap or substitution therapy and is temporary in nature.

It is, of course, not necessary to plead the cause of active immunization to the profession today. Nor is it necessary to recount to this audience the

* Read at the Cleveland meeting of the American College of Physicians April 1, 1940.

Tables 6 to 11 are from the article, "Active Immunization against Tetanus with Tetanus Toxoid," by W. W. Hall, Nav. Med. Bull., 1937, xxxv, 34–41.

Tables 12 to 14 are from the article entitled, "Active Immunization against Tetanus, Using Alum Precipitated Tetanus Toxoid," by R. Hayden and W. W. Hall, Nav. Med. Bull., 1938, xxxvi, 524–535.

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entire history of the development of toxoid immunization. Some of the high lights, however, may be briefly mentioned.

The work of active immunization against tetanus can be said to be the direct outgrowth of the method and procedure followed in the battle against diphtheria. The success attained in the fight against diphtheria by active immunization, and the value of alum-precipitated diphtheria toxoid in producing an active immunity, are attested by the complete freedom in some modern cities from the menace of childhood diphtheria.

Both diphtheria and tetanus produce soluble toxins or exotoxins. Both of these exotoxins, treated with formaldehyde and heat, become nontoxic but retain their antigenic power. These detoxified products were first called anatoxin by the French, but since then have been referred to by English-speaking nations as toxoids to avoid confusion with the word antitoxin. Both of these toxoids are precipitated by the use of alum and, though relatively insoluble when injected, gradually go into solution. Thus, antigenic stimulation is exerted little by little and over a long period of time, the recognized principle of secondary stimulation in vaccination thus being automatically employed. Antitoxin, developed as a result of this prolonged, smooth and steady action, is eventually much greater in amount than that produced by several injections of soluble and rapidly diffusible toxoid such as plain formolized toxoid.

It is understandable that immunization against diphtheria and tetanus should be coupled in our minds, because of the similarity mentioned, and because of the fact that both were developed by Ramón in the same laboratory.

Two important differences between diphtheria and tetanus, however, exist, namely: subclinical tetanus apparently does not occur and thus no natural immunity is found to exist; and there is no easy method for gauging immunity against tetanus such as the Schick test in diphtheria.

Our work on active immunization against tetanus in the U. S. Navy began in 1934 on the U. S. S. *Relief,* the fleet hospital ship. At this time the manufacture of toxoid was just beginning in this country. This investigation was designed to gather information on the optimum interval between each toxoid injection and the number of injections required for successful immunization. The study was begun using plain formol toxoid and was completed on some groups in which alum-precipitated toxoid was used exclusively.

Our observations from this study were: (*a*) that alum-precipitated toxoid was a much more efficient immunizing agent than plain toxoid: that is, it gave uniformly higher serum antitoxin titers; (*b*) the longer the interval, up to eight weeks, between the alum-precipitated toxoid injections, the better were the results obtained; and (*c*) that even very hurried immunization, such as at intervals of two weeks, gave quite titratable serum-antitoxin levels. Individuals apparently so poorly immunized by this rapid method

—surprising to us at that time—when injected with alum precipitated toxoid two to three years later, reacted within seven days with high serum antitoxin.

Another organized study of tetanus immunization in the U. S. Naval service was carried on at the U. S. Naval Academy in 1937 and reported by Hayden and Hall.[2] In this study a group of volunteers, largely football players, were immunized with alum-precipitated toxoid and the sera titrated for antitoxin. It may be interesting to note that the football players volunteered to be immunized against tetanus so that they might avoid the rather frequent serum sickness reactions which had occurred in a number of their fellow teammates after having been spiked on the field. These reactions had kept men out of play for some time and occasionally out of important games. Nine months to a year later these men were given injections of alum-precipitated toxoid and titrated before and after this repeat injection. The outstanding observation in this large group (153) was that no individual failed to respond with an adequate blood level of antitoxin, though, as in the previous *Relief* group, there were rather wide individual variations.

The final and by far the largest group studied is that which is now reported for the first time (table 5), by permission and through the courtesy of Captain R. Hayden, Medical Corps, U. S. Navy, senior medical officer during this period at the Naval Academy where the work was carried on. The entire personnel of the Academy has been immunized for the past three years. The individuals so immunized in the Naval Academy will now total 3,446.

The freedom from reactions in the use of alum-precipitated toxoid has been universally noted. Our observations have been that there is soreness of the arm, disappearing in 48 hours or sooner, from the injections which were given intramuscularly. When injections are made subcutaneously there may be a skin reaction which is greater in intensity the closer to the skin the material is placed. This is followed by a subcutaneous induration which may last, as a nodule, one or two weeks. We have chosen the intramuscular route and have made it routine in our work in the Navy, because of the relative freedom from local reaction experienced when using this route. It has been suggested that immunity is enhanced when the material is placed in the skin. This has not been our observation, for in those who have a violent skin reaction we have failed to observe any uniformly higher level in antitoxin titer than in those in whom the injection was made intramuscularly and in whom there was little or no skin reaction present. General reaction has been, with the exception to be noted later, very minor, seldom amounting to more than some malaise and an occasional minor rise in temperature of short duration.

When immunizing the midshipman personnel of the Naval Academy in 1938, 2300 men were injected. We obtained for this immunization, by purchasing in the open market, a supply of alum-precipitated tetanus toxoid made by one of the well established biological houses which had, it appeared

later, only recently begun to manufacture alum-precipitated tetanus toxoid. This toxoid had a fine physical appearance and had passed all tests for toxicity and antigenicity prescribed by the National Institute of Health.[2] We, therefore, knew that this toxoid, as well as all others licensed by the National Institute of Health, was completely detoxified and would produce no symptoms of tetanus in guinea pigs, even when injected in 10 times the human dose. We also knew that 1 c.c. would, in six weeks, produce, when injected into a 350 gram guinea pig, 2 units of antitoxin per c.c. of serum. In the first injection 2300 men were immunized. The reactions were minor and as noted in table 1.

TABLE I

Tetanus Toxoid Immunization

Naval Academy

	1938			1939	
	1st Inj.	2d Inj.		1st Inj.	2d Inj.
	Toxoid (A)	Toxoid (A)	Toxoid (B)	Toxoid (B)	Toxoid (B)
Total Injected	2300	1800	500	793	793
Total Reactions	10	50	None	1	None
Sore arms	8	38	None	0	None
Fever and malaise	2	7	None	1	None
Urticaria	1*	4	None	0	None
Anaphylaxis	0	1	None	0	None

* One month after injection.

Eight had sore arms; two had fever and malaise; one had urticaria. This urticaria occurred over a week following the injection and was thought to be due to a dietary factor at the time. Subsequently it was thought that perhaps it might not have been, and that it might justly be charged against the toxoid. In the second injection, eight weeks later, 1800 men were injected with Toxoid "A." Reactions were noted from the first, although rather minor in type. Fifty reactions were recorded in total, comprised of 38 sore arms, seven cases of fever and malaise, four of urticaria, and finally one instance of frank anaphylactic shock. The use of this toxoid was promptly stopped and the remaining 500 men were injected with another toxoid. These 500 did not have a reaction of any sort, not even one sore arm! It seems clear from the observations of these results that the Toxoid "A" contained some substance which on the first injection sensitized these men. When, after an interval of eight weeks, 1800 of them were given the second injection of toxoid, a considerable number reacted as noted. This

supposition was strongly supported when the remaining 500 men were injected with another lot of toxoid and no reaction of any type resulted (table 1).

In 1939 the incoming class of midshipmen were injected. These totaled 793. In the first injection only one reaction was noted, a fever which may or may not have been due to the toxoid. During the second injection of all these 793 men no reaction of any kind occurred. No man reported to the sick-bay for treatment. No man requested to be excused from drill formation or from class. To the medical officers, used to handling midshipmen, this seemed indeed remarkable (1939 section, table 1).

Our study of this reaction-producing toxoid presents some points of interest.

The exact structure of the tetanus toxin molecule is not known. It is, however, known to be an organic nitrogen-containing compound, nonprotein in nature. It appears to act as the deuteroproteoses, since it is precipitable by full saturation with ammonium sulphate. The toxin molecule is large and will not pass through a semi-permeable membrane.

We began our study of the nitrogen content of this reaction-producing toxoid (Toxoid "A") by comparing its nitrogen content with that of protein. It is well known that the nitrogen content of protein is approximately 16 per cent, and that amino acids and the derived proteins, being the building stones of the complete protein molecule, must approximate this 16 per cent nitrogen content. Should tetanus toxin or tetanus toxoid be of protein composition, it would approximate protein in its nitrogen content. It will be noted by reference to table 2 that the nitrogen content of the toxin

TABLE II

Study of Reaction-Producing Toxoid (A)

	Toxoid (A)	Toxoid (B)	Toxin (N.I.H.)
Organic nitrogen grams %	5.5	3.3	5.1
Protein tests	Positive	Negative	Negative

obtained from the National Institute of Health was 5.1 per cent. The toxoid which had given reactions on the second injection of 1800 men (Toxoid "A") approximated 5.5 per cent nitrogen. Toxoid "B" which was just as high in antigenic potency as Toxoid "A," and was free from reaction-producing substances, gave a nitrogen value of 3.3 per cent. Our supposition from these nitrogen values, i.e., from the high nitrogen value of Toxoid "A," higher even than the highly potent toxin of the National Institute of Health, and from our clinical observation, was that Toxoid "A" contained a protein substance. As protein contains 16 per cent nitrogen it would, if mixed with the toxoid, raise its nitrogen content in proportion to the amount

of protein present. We also ran certain protein tests,* with results in general as noted in table 2: positive with Toxoid "A," negative with Toxoid "B," and negative with the National Institute of Health toxin.

The evidence just cited suggested that we should be able to sensitize guinea pigs and be able to shock and perhaps produce anaphylactic death by using the toxoid which appeared to contain a sensitizing substance. Rather surprising results were obtained. In the first place the reinjection of alum-precipitated tetanus Toxoid "A" into guinea pigs sensitized by a previous injection of this toxoid produced no anaphylaxis. For this we had no explanation unless there was too small an amount of the substance in soluble form in the supernatant fluid. What was noted is recorded in table 3.

Guinea pigs were injected with alum-precipitated tetanus toxoid. After an interval of time they were injected with another dose of alum-precipitated tetanus toxoid; no reaction occurred. But, when injected with crude tetanus toxoid, pigs from this lot died in anaphylaxis. Could this be due to a broth protein which had been carried over and was producing sensitization? To test this, pigs from the same lot were injected with *crude diphtheria* toxoid from the same type broth; no reaction occurred. Then the picture was reversed; we used a set of guinea pigs sensitized by injecting alum-

* Reactions for proteins.

Test	Toxin (NIH)	Toxoid "A"	Toxoid "B"	Test specific for:
Biuret reaction	Negative	Weak positive	Negative	($CO.NH_2$) Carbamyl group
Ninhydrin reaction	Weak positive	Slight positive	Weak positive	Amino-acids, peptides, proteins. All acids having a free amino group in the alpha position.
Glyoxylic acid reaction	Negative	Positive	Negative	Tryptophan nucleus.
Molisch-Udransky reaction	Positive	Positive	Positive	Specific for carbohydrate group.
Hydrochloric acid and heat test	Negative (No color)	Positive (Deep purple)	Positive (No color)	Positive when protein is present with toxoid.

The hydrochloric acid and heat test may represent a new observation. We have not been able to locate such a test in the literature. Credit for this observation should be given Chief Pharmacist P. S. Gault, U. S. Navy. It appears to depend upon the simultaneous presence of a formolized tetanus toxoid molecule and a protein molecule, such as serum albumin. Specimens of toxoid which reacted negatively to this test were mixed with blood serum and used as positive controls.

The washed and dried alum-precipitated tetanus toxoid was treated with concentrated hydrochloric acid to convert it to a water-soluble form. Toxoid "A" dissolved with the formation of a deep purple color; whereas Toxoid "B" dissolved without the formation of the purple color.

Another portion of Toxoid "B," to which blood serum had been added, was treated with concentrated hydrochloric acid; a deep purple color was produced. Prior to the addition of the hydrochloric acid, the dried toxoid-serum mixture was evaporated to dryness on a water bath.

TABLE III

Sensitization of Guinea Pigs with Toxoid

Pigs injected with			
A.P. Tetanus Toxoid	Time Interval	A.P.T. Tetanus Toxoid	No Reaction
A.P. Tetanus Toxoid	Time Interval	Tetanus Toxoid Crude	Death
A.P. Tetanus Toxoid	Time Interval	Diphtheria Toxoid Crude (Same Broth)	No Reaction
A.P. Diphtheria Toxoid	Time Interval	Diphtheria Toxoid Crude	Death
A.P. Diphtheria Toxoid	Time Interval	Tetanus Toxoid Crude (Same Broth)	No Reaction

TABLE IV

Tetanus Toxoid Immunization

Showing follow-up titrations on some 6 year cases

1–2 (Relief)	
June 1934	—1 dose plain tetanus toxoid.
Dec. 1934	—2 doses alum precipitated tetanus toxoid. (8 weeks interval)
Dec. 4, 1935	—Titer, 0.1 unit
Dec. 5, 1935	—4th dose alum precipitated tetanus toxoid.
Dec. 12, 1935	—Titer, >3.0 <5.0 units.
Jan. 4, 1940	—Titer, 0.1 0.5 unit.
V–117 (Relief)	
Feb. 8, 1935	—2 doses (6 weeks interval) alum precipitated tetanus toxoid.
Nov. 5, 1935	—Titer, 0.04 unit.
Nov. 5, 1935	—3rd dose alum precipitated tetanus toxoid.
Nov. 12, 1935	—Titer, 10.0 15.0 units.
Jan. 4, 1940	—Titer, 0.5 1.0 unit.
Jan. 4, 1940	—4th dose alum precipitated tetanus toxoid.
Jan. 12, 1940	—Titer, 15.0 units.
V–124 (Relief)	
Feb. 28, 1935	—2 doses (6 weeks) alum precipitated tetanus toxoid.
Nov. 5, 1935	—Titer, 0.01 unit.
Nov. 5, 1935	—3rd dose alum precipitated tetanus toxoid.
Nov. 12, 1935	—Titer, 10.0 15.0 units.
Jan. 4, 1940	—Titer, .5 1.0 unit.
Jan. 4, 1940	—4th dose alum precipitated tetanus toxoid.
Jan. 12, 1940	—Titer, 12.0 units.
IV–46 (Relief)	
June 1934	—3 doses (6 weeks interval) plain tetanus toxoid.
June 1936	—Titer, 0.01 unit.
June 1936	—1 dose alum precipitated tetanus toxoid.
June 1936	—(7 days later) Titer, 0.25 0.5 unit.
Jan. 4, 1940	—1 dose alum precipitated tetanus toxoid.
Jan. 4, 1940	—Titer, 0.3 unit.
Jan. 12, 1940	—Titer, 10.0 units.

precipitated diphtheria toxoid. No reaction occurred when these pigs were injected with alum-precipitated diphtheria toxoid but they died of anaphylactic shock when injected with *crude diphtheria* toxoid. Yet no reaction occurred when others from the same lot were injected with *crude tetanus* toxoid from homologous broth. We wish to thank Dr. W. T. Harrison of the National Institute of Health for help in this phase of the study.

These results clearly indicate that alum-precipitated toxoid contains sensitizing and immunizing fractions. If an injection of either diphtheria

TABLE V

Tetanus Toxoid Immunization

Titration Naval Academy Immunees

1937–1940

Group no.	Injection dates			Antitoxin per c.c. serum	
	1st	2d	3d	Date of bleeding 1/20/40	
A-1	4–1–37	6–2–37	9–7–37	>0.05	<0.1
A-2	9–10–37	10–26–37	3–7–38	0.01	0.05
A-3	4–1–37	6–2–37	9–7–37	0.01	0.1
A-4	4–1–37	6–2–37	9–7–37	0.01	0.05
A-5	4–1–37	6–2–37	9–7–37	0.01	0.05
A-6	4–1–37	6–2–37	9–7–37	0.1	
A-7	4–1–37	6–2–37	9–7–37	0.01	0.05
A-8	4–1–37	6–2–37	9–7–37	0.01	0.05
A-9	4–1–37	6–2–37	9–7–37	0.1	0.5
A-10	4–1–37	6–2–37	9–7–37	0.01	0.05
A-11	4–1–37	6–2–37	9–7–37	0.01	0.05
A-12	4–1–37	6–2–37	9–7–37	0.1	
B1-1	9–27–38	12–7–38		0.08	
B1-2	9–27–38	12–7–38		0.5	
B1-3	9–27–38	12–7–38		0.01	0.05
B1-4	9–27–38	12–6–38		0.05	0.1
B1-5	9–29–38	12–6–38		0.07	
B1-6	9–29–38	12–6–38			0.05
B2-1	3–29–38	5–27–38	9–27–38	0.1	0.5
B2-2	3–29–38	5–27–38	9–27–38	0.1	0.5
B2-3	3–5–38	9–10–38	9–27–38	0.01	0.05
B2-4	3–29–38	9–27–38	12–6–38	0.5	
B2-5	3–29–38	5–27–38	9–28–38	0.1	0.5
B2-6	3–29–38	5–31–38	10–10–38	0.1	0.5
C-1	8–17–39	9–23–39		0.1	0.3
C-2	8–15–39	9–21–39		0.05	0.1
C-3	8–17–39	9–23–39		0.8	1.0
C-4	8–17–39	9–23–39		0.1	0.2
C-5	8–17–39	9–23–39		0.1	0.3
C-6	8–15–39	9–21–39		0.1	0.5
C-7	8–15–39	9–21–39		0.3	
C-8	8–15–39	9–21–39		0.1	0.2
C-9	8–17–39	9–23–39		0.1	0.3
C-10	8–17–39	9–23–39		0.5	
C-11	8–17–39	9–23–39		0.4	0.5
C-12	8–15–39	9–21–39		0.1	0.3

or tetanus alum-precipitated toxoid is followed by an injection of the homologous crude toxoid, a sufficient dose of the shock-producing substance is present, in soluble form, to produce a reaction. This conclusion also appears clear: an alum-precipitated toxoid, thoroughly washed, is a safe immunizing agent. Crude toxoid is not, although it should be remembered that that which can produce anaphylactic reactions in guinea pigs does not react with equal severity in man. However, crude toxoid, on second and third injections, may produce reactions of sensitization, while well prepared alum-precipitated toxoid should not.

On further investigation it was found that the alum-precipitated toxoid "A," which had produced reaction in our group in the Naval Academy with the second injection, had been prepared in such a manner that it probably

was inadequately washed. After throwing down the precipitate in a centrifuge it had been taken up in an equal amount of saline according to the proper technic, but it had been placed in large jars and hand-shaken. The same shaking had been employed in each repeat washing. Toxoid "B" had been prepared in essentially the same way, but with one important difference. It had been mechanically agitated in an electrically driven churn arrangement. We believe that therein lay the explanation of the reactions produced in our Naval Academy group, i.e., inadequately washed alum-precipitated toxoid.

We have gone thus at length into the discussion of this reaction-producing toxoid to emphasize the fact that alum-precipitated tetanus toxoid, if properly manufactured, does not result in reaction on injection or reinjection, rather than to dwell upon the reactions which are here recorded, since these reactions with one exception were not serious in nature. We wish to emphasize the fact that they would not have occurred at all if the toxoid had been properly washed and prepared.

Tetanus toxoid immunization is now receiving world-wide acceptance. Tetanus toxoid immunization has been compulsory in the French army for more than five years. No case of tetanus has yet been reported in that time in any immunized individual. Tetanus toxoid immunization of the French cavalry horses has also been carried out for the last six years.[8] Prior to their immunization with tetanus toxoid the tetanus toxoid in these animals had been approximately 0.4 per cent over a period of six years. Thus, in 16,000 immunized horses there would have been, if unimmunized, 164 cases of tetanus. There were, in fact, none during this entire period. In more than a million persons vaccinated during military service, no serious accident was noted nor any case of tetanus. In 1937 the Italian army adopted tetanus toxoid immunization and in 1938 the English army adopted this immunization. The present war will probably yield new proof of the immunizing effect of anatoxin or toxoid.

Titrations which are given in the tables which follow are taken from the U. S. Navy groups from 1934 to 1940, the largest single compilation of immunees so studied in the United States. These serum-antitoxin titration results are supported by similar results published by numerous American and European workers.[9, 10, 11] But more important, it is felt, in the proof of the dependability of tetanus toxoid immunization, is the experience of the large immunized groups who remain free of tetanus.[12, 13]

The 53 men in group I were given two injections of alum-precipitated tetanus toxoid, 0.5 cubic centimeter each, 8 weeks apart, as basic immunization. They were then given an injection of 0.5 cubic centimeter of A. P. T. T. 14 weeks later. Just before this stimulating or pick-up injection, blood was drawn for antitoxin titration (titration A), and 1 week afterward another titration was made (titration B).

The 77 men in group II were given two injections of alum-precipitated tetanus toxoid, 0.5 cubic centimeter each, 8 weeks apart, as basic immunization. They were then given an injection of 1.0 cubic centimeter of A. P.

TABLE VI

Group I.—*Antitoxin titrations* (U. S. S. *Relief*)

[Units per cubic centimeter of serum]

Volunteers no.	A	B	C*	D	E	F
2–I	0.01	0.20	0.50	0.04	0.01–0.04	3– 5.0
5–I	.01	0.10– .20	1.0	0.10– .25	.01– .25	1.0
6–I	.01	.20– .50		.25	.25	5– 8.0
13–I	.01	.50–1.0		.50	.50	3– 4.0
15–I	.01	.50–1.0	1.00–2.0	.25	.25	5– 7.0
17–I	.01	2.0	2.00–3.0	.25	.25	5–10.0
19–I	.01	.20– .50	.50–1.0	.10– .25	.10	3.0
24–I	.01			.10	.10– .25	3– 5.0
29–I	.01	.50–2.0	1.00–2.0			
Average	.01	.78	*1.30	.217	.215	4.40

1 cubic centimeter of old toxoid given as "sensitizing" dose, 8 months' rest, then 2 doses of alum-precipitated toxoid with 6-week interval between doses. Titration before each dose (A and B) and 10 weeks after second dose of alum-precipitated toxoid (C*). Finally 17 months after initial injection or 8 months after third injection, a dose of alum-precipitated toxoid was given with titrations before (D), 2 days after (E), and 7 days after the injection (F).

* The titration giving the highest average response to the basic immunization is indicated by asterisk (*).

TABLE VII

Group II.—*Antitoxin titrations* (U. S. S. *Relief*)

[Units per cubic centimeter of serum]

Volunteers no.	A	B	C*	D	E	F	G
11–II	0	0.001	0.01–0.20	0.04	0.01–0.04	0.01–0.04	2 –3.0
14–II	0	.001	.01– .04	.01– .04	.01– .10	.01	.5–1.0
25–II	±	.005	.10	.04– .10			
33–II	0	.001	.01– .10	.04– .10			
38–II	0		.02		.01	.04	1 –2.0
40–II	±	.002	.01– .04				
41–II	0	.001	.10	.04– .10	.04	.04	3 –5.0
43–II	0		.01	.01– .04	.04	.04	3 –5.0
Average	±	.002	*.055	.05	.035	.031	2.550

3 doses (1 c.c. each) of old toxoid; 5-week interval between first and second, and 6-week interval between second and third were given in the basic course.

Titration.—A, 5 weeks after first dose (just before second was given); B, 6 weeks after second; C*, 24 weeks after third; D, 35 weeks after third; E, 17 months after first or approximately 14 months after completion of course of 3 injections. At this time (17 months after first injection) an injection (1 c.c.) of alum-precipitated toxoid was given, following which titrations were made at 2-day interval (F) and 7-day interval (G).

* The titration giving the highest average response to the basic immunization is indicated by asterisk (*).

TABLE VIII

Group II (A).—*Antitoxin titrations* (U. S. S. *Relief*)

[Units per cubic centimeter of serum]

Volunteers no.	A	B	C	D
70–II (A)	0	0.01		0.04–0.10
82–II (A)	±	.04	0.10–0.20	.10– .25
95–II (A)	±	0.10– .25	.10– .20	.04– .10
Average	±	.070	.15	.10

3 injections (1 c.c. each) of old toxoid; 8-week interval between first and second injections, 6-week interval between second and third.

Titrations.—A, 8 weeks after first dose; B, 6 weeks after second dose; C, 19 weeks after third dose; D, 49 weeks after third dose.

TABLE IX

Group III.—*Antitoxin titrations* (U. S. S. *Relief*)

[Units per cubic centimeter of serum]

Volunteers no.	A	B	C	D	E*	F	G	H
12–III	0	0.0004	0.040			0.01	0.10–0.250	3–5.0
44–III	0	.005	.010–0.10			.010–.04	.01–.040	5.0
45–III	0	.001	.01	0.01	0.01			
47–III	0	.020	.010–.04					
48–III	±	.002	.01	.04				
49–III	0	.005	.100–.25	.01–.10				
50–III	0	.005	.010		.04			
53–III	±		.010–.10		.040–.10			
54–III	0	.001	.010	.010–.10	.010–.04	.010–.04	.02	3.0
55–III	±	.002	.040	.010–.02	.040–.10			
56–III	0		.010	.010	.01–.04			
101–III	0	.001	.010	.020	.010–.04			
Average	±	.004	.035	.030	*.053	.050	.070	4.0

Three doses of old toxoid; 6-week interval between first and second injections and 2-week interval between second and third injections were given in basic course.

Titrations.—A, 6 weeks after first dose (just before second was given); B, 2 weeks after second dose (just before third was given); C, 6 weeks after third dose; D, four months after third dose; E*, 10 months after third dose; F, 17 months after first dose and just before an injection of 1 cubic centimeter of alum-precipitated toxoid; G, 2 days after the dose of A.P.T.; H, 7 days after the dose of A.P.T.

* The titration giving the highest average response to the basic immunization is indicated by an asterisk (*).

TABLE X

Group IV.—*Antitoxin titrations* (U. S. S. *Relief*)

[Units per cubic centimeter of serum]

Volunteers no.	A	B	C*	D	E	F	G
16–IV	0	0.00040		0.010	0.010	0.040–0.10	3–5.0
46–IV	±	.00100	0.010–0.04	.010–.04	.010	.010	.25– .5
Average	±	.00070	.025	.017	.010	.040	2.180

Three doses of old toxoid with 2-week intervals between first and second doses, and between second and third doses, were given in basic course.

Titrations.—A, 2 weeks after first dose; B, 2 weeks after second dose; C, 2 weeks after third dose; D, 10 months after third dose; E, 17 months after first and 16 months after third dose, and just before an injection of A.P.T.; F, 2 days after dose of A.P.T.; G, 7 days after dose of A.P.T.

* The titration giving the highest average response to the basic immunization is indicated by an asterisk (*).

TABLE XI

Group V.—*Antitoxin titrations* (U. S. S. *Relief*)

[Units per cubic centimeter of serum]

Volunteers no.	A	B*	C	D	E
108–V	0.010	0.10–0.50	0.010–0.040	0.040	3– 5.0
111–V	.010	.25– .50	.010– .040	.010	2.0
112–V	.010	.25– .50	.040	.010–.04	5– 8.0
117–V	.010	1.0	.040– .10	.040	10–15.0
120–V	.010	.50–1.0	.040	.040	8.0
121–V	.010	.5	.040	.040	8.0
122–V	.010	.10– .25	.010– .04	.010–.04	3– 5.0
124–V	.010	.50–1.0	.040	.010–.04	15–25.0
129–V	.010	.10	.040	.010–.04	5– 8.0
131–V	.010	.50–1.0	.010– .04	.010–.04	10.0
133–V	.010	.10– .25	.010– .04	.010	1.0–2.0
134–V	.010–.10	.5	.110	.10	25–50.0
136–V	0.1	.25– .50	.010	.010	3– 5.0
Average	.010	*.40	.039	.032	9.60

Two doses of alum-precipitated toxoid (A.P.T.) with 6-week interval between injections in basic course.

Titrations.—A, 6 weeks after first injection; B, 6 weeks after second injection; C, 9 months after first injection and just before the final repeat or stimulation dose of A.P.T.; D, 2 days after repeat dose of A.P.T.; E, 7 days after repeat dose of A.P.T.

* The titration giving the highest average response to the basic immunization is indicated by an asterisk (*).

TABLE XII

Group I—*53 subjects* (Naval Academy, 1938)

[Units of antitoxin per c.c. of blood serum]

No.	Titration A	Titration B	No.	Titration A	Titration B
I–1	>0.025–<0.05	0.1	I–29	.025	.1
I–2		.1	I–30	>.075–<.1	.25
I–3	>.1 – <.15	.75	I–31	.025	.1
I–4	>.025– <.05	.1	I–32	>.1 –<.15	.25
I–5	>.075– <.1	.1	I–33	>.1 –<.15	>1.0 –<1.5
I–6	>.075– <.1	>.75 –<1.0	I–34	.025	>.075– <.1
I–7	>.075– <.1	.1	I–35	.025	.1
I–8	>.025– <.05	>.075– <.1	I–36	.1	.5
I–9	>.05 – <.075	.25	I–37	.075	.25
I–10	.025	.1	I–38	>.1 –<.15	.5
I–11	>.075– <.1	>1.0 –<1.5	I–39	.075	.25
I–12	<.01	>.075– <.1	I–40	>.1 –<.15	.75
I–13	>.1 – <.15	>.25 – <.5	I–41	>.1 –<.15	.75
I–14	.025	.25	I–42	.075	.25
I–15	.025	.1	I–43	.075	.75
I–16	.025	>.1 – <.25	I–44	.1	>1.0 –<1.5
I–17	>.05 – <.075	2.0	I–45	.025	.1
I–18	.05	>.1 – <.25	I–46	.1	.5
I–19	>.01 – <.025	.1	I–47	.025	>.075– <.1
I–20	>.075– <.1	>1.0 –<1.5	I–48	.075	.1
I–21	.025	.1	I–49	.1	.5
I–22	.05	.5	I–50	.075	>.25 – <.5
I–23	.075	>.5 – <.75	I–51	.05	.5
I–24	.05	.1	I–52	.025	>.75 –<1.0
I–25	>.1 – <.15	>.25 – <.5	I–53	>.1 –<.15	>1.0 –<1.5
I–26	<.01	>.075– <.1			
I–27	.075	>.5 – <.75	Average	.062	.433
I–28	.025	.5			

NOTE.—The sign (>) means greater than; and the sign (<) means less than.

TABLE XIII

Group II—*77 subjects* (Naval Academy, 1938)

[Units of antitoxin per c.c. of blood serum]

No.	Titration A	Titration B	No.	Titration A	Titration B
II–54	0.025	0.25	II–94	.01	.5
II–55	.075	1.0	II–95	.025	.25
II–56	.05	.25	II–96	.1	>1.0 –<1.5
II–57	>.05 – <.075	.75	II–97	.05	.1
II–58	.05	.75	II–98	>.05 –<.075	.5
II–59	>.05 – <.075	.5	II–99	.025	.5
II–60	.05	.75	II–100	.075	.75
II–61	.025	>.75 –<1.0	II–101	>.1 –<.15	.25
II–62	.05	.5	II–102	.05	.5
II–63	.05	.25	II–103	.1	>2.0 –<2.5
II–64	.025	1.0	II–104	<.01	.1
II–65	.05	.5	II–105	>.1 –<.15	1.0
II–66	>.075– <.1	1.0	II–106	.05	1.0
II–67	.025	.25	II–107	.05	.5
II–68	>.1 – <.15	>2.0 –<2.5	II–108	.075	1.0
II–69	>.1 – <.15	>1.0 –<1.5	II–109	.05	.25
II–70	<.01	.1	II–110	.1	.25
II–71	>.025– <.05	.25	II–111	.05	.1
II–72	>.1 – <.15	1.0	II–112	.01	.25
II–73	>.025– <.05	1.5	II–113	>.025–<.05	>.25 – <.5
II–74	.1	1.0	II–114	>.05 –<.075	1.0
II–75	.01	.25	II–115	.1	.5
II–76	.01	.25	II–116	.1	1.0
II–77	.025	.5	II–117	.075	.25
II–78	>.05 – <.075	>2.0 –<2.5	II–118	.075	.75
II–79	>.01 – <.025	.1	II–119	.05	.25
II–80	.075	.5	II–120	.025	.75
II–81	.01	.5	II–121	.05	.75
II–82	.025	>1.0 –<1.5	II–122	.025	>.075– <.1
II–83	>.025– <.05	>.075– <.1	II–123	>.1 –<.15	1.0
II–84	.1	>2.0 –<2.5	II–124	.01	.25
II–85	>.1 – <.15	>2.0 –<2.5	II–125	.05	.75
II–86	.05	1.5	II–126	.025	.25
II–87	.075	>2.0 –<2.5	II–127	.05	>.25 – <.5
II–88	.025	.25	II–128	.025	.5
II–89	.05	.75	II–129	.1	1.0
II–90	.025	1.0	II–130	.01	.25
II–91	.1	1.5			
II–92	.1	.5	Average	.055	.684
II–93	.025	.1			

T. T. 19 weeks later. Just before this stimulating or pick-up injection, blood was drawn for antitoxin titration (titration A), and 1 week afterward another titration was made (titration B).

What is the minimum antitoxin level necessary for protection against tetanus? Many attempts have been made to determine this level in animals. Gold [14] arbitrarily chose a level of 0.1 unit per c.c. as the level necessary for protection. We [1, 2] have shown in repeated cases that individuals with a serum-antitoxin level of only 0.01 unit per c.c. of serum respond rapidly with high blood antitoxin levels upon toxoid stimulation. Toxin will naturally produce the same stimulation. The antigenicity of toxoid and toxin are the same. The toxicity only has been changed by formolization. Tetanus infection would thus produce the same stimulus necessary to anti-

TABLE XIV

Group III—*22 subjects* (Naval Academy, 1938)

[Units of antitoxin per c.c. of blood serum]

No.	Titration A	Titration B	No.	Titration A	Titration B
III–131		0.1	III–144		>.1– <.5
III–132		>.1–<0.5	III–145	.5	
III–133	>0.05–<0.1	>.1– <.5	III–146	.05	<.5
III–134		.5	III–147		1.5
III–135	>.1– <.25	1.0	III–148	.25	.5
III–136		.1	III–149	.1	>.5–<1.0
III–137	<.05	.5	III–150	>.05–<.1	.5
III–138	.1	<.5	III–151	.25	.5
III–139		.1	III–152	.05	.5
III–140	>.05– <.1	1.0	III–153		1.5
III–141		>.5–<1.0			
III–143	.1	1.0	Average	.140	.552

toxin formation and produce it in an ideal manner—progressively as the organisms multiply.

Bergey, Brown and Etris[15] have shown that circulating antitoxin does not measure the total protection, the tissue immunity being considerably greater. They also have demonstrated in animals that 0.01 unit antitoxin per c.c. is amply protective. Even such figures, probably, are not a measure of the minimum protective level; there may be no minimum. "Once immunized always protected" may some day be proved. Dr. W. T. Harrison of the National Institute of Health well expressed the thought that basic tissue immunity, not titratable humoral immunity, is of prime importance when he said (personal communication) "As far as I am aware, there are no figures available which will indicate the antitoxin level necessary to prevent tetanus. The most important factor, it seems to me, is the development of a situation within the body which will permit rapid formation of antitoxin, should it become necessary."

The majority of our titrations, following repeat injections, have been made at the end of one week. This was not done because of the fact that we felt that the antitoxin curve had reached its height at this time but to demonstrate the rapidity of rise of antitoxin. An Ensign, who had been immunized in the Naval Academy, was injured after graduation in an automobile accident which occurred a year and a half after his immunization. We obtained a specimen of blood serum which showed a level of slightly less than 0.1 unit of antitoxin per c.c. He was then injected with 1 c.c. of alum-precipitated tetanus toxoid, and one week later a specimen of blood was obtained. This second specimen showed an antitoxin level of 2 units per c.c. Two months following this, another specimen of blood was obtained, his blood at that time showing an antitoxin level of 12 units per c.c. This observation illustrates the rising curve of antitoxin in those individuals who have a basic or tissue immunity.

It is surely not necessary to recommend tetanus toxoid immunization by citing the accidents which occur in the use of antitoxin: i.e., serum sickness, anaphylaxis, and the like. Yet it may be noted that many of the cases which have been referred to us for tetanus toxoid immunization have been those who have experienced the most severe reactions when taking antitoxic serum, and yet experienced no untoward reaction upon injection of toxoid. The group of allergic patients, asthmatics and hay fever sufferers, should also be an important one for the use of toxoid in civilian life.

The combination of tetanus toxoid with diphtheria toxoid, which is highly successful in the immunization of children, is not desirable for use in the Navy. Diphtheria is not a problem in adults; and it is well to avoid the reactions incident to the use of diphtheria toxoid in adults.

It is felt that the introduction of toxin by other routes, such as nasal drops, is not sufficiently positive to be relied upon, even though it has been demonstrated that antitoxin does rise after application of toxoid to the nasal mucosa.[14] A subcutaneous or intramuscular injection is slightly if any more uncomfortable than a nasal swabbing.

In the light of available data, the present minimum protective plan which we in the Navy contemplate is obviously far more comprehensive than is necessary. At present, it seems wise to over- rather than under-immunize. Later, in the use of tetanus toxoid immunization, it may be determined how close one can run to the lower margin of safety. Our plan is that after the basic immunization with two injections of alum-precipitated tetanus toxoid eight weeks apart, a man, when wounded, receives an injection of toxoid; and all cases regardless of injury, once having been immunized, receive an injection of toxoid every four years thereafter. Doses subsequent to the first injection act as a stimulating or booster dose, raising both the humoral and tissue immunity. Illustrations of this fact can be found in all our tables, particularly in table 4, in which a few of the men who were immunized in 1934–36 were titrated before, and a week after, a dose of toxoid given in January 1940.

It may be of interest here, to quote a section from "Tetanus in War Time." [2]

"The importance of tetanus in civil life may be small. In warfare, however, the conditions which minimize the importance of tetanus in civil populations are completely reversed, and high incidence of tetanus, with its great mortality rate, becomes a major medical problem. In civil life wounds are few, often superficial and uncontaminated, and antitoxin is quickly available. War wounds, on the other hand, are notably deep, with much devitalized tissue and soil contamination, and serum is often not promptly available.

"The accompanying table shows the important rôle tetanus has played in modern wars.

"It will be noted that the incidence of tetanus has varied considerably according to the type of war and the soil pollution in the theater of war.

Tetanus in Modern Wars

Military Force	Date	Incidence per 1000 wounded	Mortality (per cent)
British Legion in Spain	1833–40	12.5	88.2
British in Turkey and Crimea	1854–56	1.5	82.1
Italian War with Austria	1859–61	10.0	92.4
American Civil War	1860–65	2.0	89.3
German in Franco-Prussian War	1870–71	3.5	90.0
British Expeditionary Force in France and Belgium	1914	5.2	—
British Expeditionary Force.....Total	1915–19	1.5	50.0
German-all fronts	1914	3.8	75.0
United States in France and United States of America	1917–18	0.2	11.1

Prior to the World War, in those who contracted tetanus, the mortality rate was close to 90 per cent. In the German army, during 1914, when troop movements were rapid and lines not stabilized, the incidence was high and the mortality reminiscent of the Franco-Prussian War. When lines were stabilized, and medical service prompt and efficient, the incidence of tetanus dropped to 0.8 per thousand in the German forces, and 0.2 per thousand in the United States troops, with case mortality in the United States cases as low as 11.1 per cent.

"In view of the results to be anticipated from active immunization against tetanus—namely, that the general use of this method would definitely prevent almost every case of tetanus—even the low rates for tetanus prevailing in the closing years of the World War are far too high.

"Neither the location nor type of our future operations is known. Wherever they may be, delay in antitoxin administration would certainly cause increased tetanus. Such delay is favored by the speed and range of our air and surface craft, the use of small groups of men in landing forces, and by the trends in aviation and in ground mechanization of troops,—all of which are factors tending toward wide range of action and consequent remoteness from base medical attention."

The case for tetanus toxoid immunization has been ably and very completely presented by many writers.[16, 17, 18] The uniformity of satisfactory immunization, the freedom from untoward reactions, and the thermostability of alum-precipitated tetanus toxoid have all been well documented. In this discussion, designed particularly to recount our experiences with toxoid immunization in the United States Navy, further repetition or amplification of these points is not necessary.

Likewise, it is unnecessary to dilate upon the disadvantages of the use of antitoxin. We all recognize the fact that when properly and promptly used antitoxin prevents all but a few cases of tetanus and that only those which develop unrecognized die in spite of antitoxin. It is well known that antitoxin, when injected prophylactically, protects only for a relatively short time and that the steadily falling curve of antitoxin in the blood reaches zero in about two weeks after an injection. We also recognize the dangers

and discomforts of serum sickness and allergy. In spite of these shortcomings and disadvantages, tetanus antitoxin will probably never be entirely discarded. There will always be a large number of individuals who are not immunized: millions of patients and many doctors who operate by hindsight rather than foresight. Nevertheless, tetanus toxoid immunization is so completely fitted to our needs in the military services, and to all other groups which can be well controlled medically, that its universal adoption, under such control, seems inevitable.

Summary

1. Immunization with tetanus toxoid has been studied in the U. S. Navy since 1934. Volunteer groups were used at first.

2. Active immunization against tetanus, by means of plain or alum-precipitated tetanus toxoid, is a safe and reliable procedure.

3. With properly prepared toxoid, reactions are minor and infrequent. We report some reactions encountered when using a certain toxoid, the reactions probably being caused by inadequate washing of the alum-precipitated toxoid during preparation.

4. Toxoid immunization has now been adopted by the French, Italian and British armies.

5. No case of tetanus in a toxoid immunized individual has yet been reported.

6. The actual antitoxin level in the blood is not of prime importance. Basic immunity, or ability of tissue to react with the production of antitoxin, is the essential condition.

7. The present plan, in use in the Navy, is two injections eight weeks apart as basic immunization; injection at the time of injury if deemed necessary to raise blood antitoxin rapidly; injection each four years after basic immunization to maintain immunity at a high level.

8. All midshipmen at the U. S. Naval Academy are now routinely immunized with alum-precipitated tetanus toxoid. More than 3400 have been so protected, as well as many other navy personnel and dependents.

9. Toxoid immunization, against tetanus, is ideally fitted to the needs of the military services and to all other groups which can be medically well controlled.

10. Its universal adoption in such groups seems inevitable.

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AN ANALYSIS OF 200 PATIENTS EXAMINED GASTROSCOPICALLY *

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It has often been stated that the enthusiasm which attends the introduction of a new therapeutic or diagnostic agent is short-lived unless that agent fulfills certain requirements. In general these requirements are safety, simplicity and ease of employment, and finally, results that are dependable and of value.

It is the purpose of this paper to report on these facts as they apply to gastroscopy performed with the Wolf-Schindler flexible gastroscope in the Bronchoscopic Department of the Jefferson Hospital. It is hoped that such an analysis, added to the rather large number of studies already made, will be of value in establishing the exact status of this procedure.

The literature, both in this country and abroad, amply attests the safety of flexible tube gastroscopy. This safety is truly remarkable in comparison with the high incidence of morbidity, and even mortality, resulting from the older form of gastroscopy with the rigid instrument. Although one hears from time to time of a death attributed to this new diagnostic method there is not a single case reported in the literature to my knowledge. In a recent communication Dr. Schindler corroborated this statement, as did Moutier, Gutzeit and Henning six months ago. In our experience at the Jefferson Hospital, where flexible tube gastroscopy has been employed for over three years, no mortality has been encountered and the morbidity has been nil.

Gastroscopy with the flexible instrument is the most readily performed of all endoscopic examinations. Dr. Schindler has always insisted that it is primarily an office or clinic procedure. We have never found it necessary to hospitalize a patient for gastroscopic examination alone. Moreover, in the majority of patients the only preparation that we now employ is to have the patient present himself fasting and then have him gargle with a 2 per cent Pantocain solution. This is followed by a brief, gentle swabbing of the pharynx with the same solution on a cotton tampon. Following anesthetization the patient is placed on his left side on a table and the gastroscope passed. The average length of time for the examination is five minutes. After the examination the patient is at liberty to leave the hospital and resume whatever activity he wishes. Therefore, it is felt that the second requirement, namely simplicity and ease of employment, is adequately fulfilled.

To demonstrate the value of flexible tube gastroscopy two hundred patients have been selected in whom a fractional gastric analysis, roentgen-ray and gastroscopic examination had been performed. The group is composed

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of ward and clinic patients on whom routine studies were made. An attempt has been made to correlate the findings with the patient's history.

Of the two hundred patients we examined there were 133 males and 67 females; the youngest was 15, the oldest 75, and the average age 37 years. In each of 128 patients a definite lesion was seen in the stomach and the following diagnoses were made; gastritis in 51, cancer in 42, peptic ulcer in 29, and benign polyp in 6. In 72 patients no stomach lesion was found.

Cancer. Schindler and Templeton [1] state that in the case of neoplasm of the stomach the roentgen-ray and gastroscopic diagnoses usually agree. Schloss, Ettinger and Pratt [2] also hold this opinion and Schatzki [3] believes that gastroscopy is a definite adjunct in diagnosing cancer of the stomach where the roentgen-ray diagnosis is uncertain or incorrect. Our findings agree with these opinions.

Of the 42 patients having cancer 70 per cent were male and 30 per cent female. Sixty-eight per cent gave a history of gnawing pain in the epigastrium occurring between meals, anorexia, inability to take solid food, and loss of weight. The gastric analysis in 66 per cent of these patients showed a low total and no free hydrochloric acid, and there was occult blood in all specimens.

The gastroscopic and roentgen-ray diagnosis was the same or similar in 71 per cent of the patients having cancer. In 62 per cent the diagnosis was confirmed by a microscopic study of sections secured at operation or necropsy. In three instances in which there was negative roentgen-ray evidence the lesion was diagnosed by gastroscopy and in five with negative gastroscopic evidence the diagnosis was made by roentgen-ray. The gastroscopic examination was unsatisfactory in four of these patients due to lack of cooperation.

Peptic Ulcer. A peptic ulcer was found in each of 29 patients, twenty-eight male and one female. The youngest patient in this group was 20, the oldest 65, and the average age 40 years. The symptoms in 58 per cent of these patients included epigastric pain occurring one to two hours after meals, and at night, sour eructations, nausea and vomiting. Usually relief from these symptoms was obtained after taking alkalies. Fractional gastric analysis showed hyperacidity in 33 per cent of these patients, with occult blood in all specimens.

Regarding the respective merits of the methods of diagnosing gastric ulcer Schatzki [3] concludes that large ulcers are more easily diagnosed by roentgen-ray, whereas small ulcers may be missed on roentgen-ray examination but can usually be seen gastroscopically; while Schloss, Ettinger and Pratt [2] feel that ulcers are more frequently discovered by gastroscopy than by roentgen-ray. Palmer, Templeton and Schindler [4] studied a series of 50 patients having gastric ulcer with careful roentgen-ray compression technic and gastroscopy and their comparative findings showed that the diagnoses were identical by both methods in 32 patients, and that they were made by

roentgen-ray only in 8 patients and by gastroscopy only in 6 patients. In four instances the patient was not gastroscoped so that the diagnosis was made entirely by roentgen-ray. Our own findings in gastric ulcer closely approximate the above.

The diagnoses made by roentgen-ray and gastroscopy were the same in 55 per cent of the patients having peptic ulcers. We considered the diagnosis confirmed in 65 per cent of the patients when they improved and were completely free of symptoms following medical management for gastric ulcer. The diagnosis was proved in four instances at operation and in one case was not confirmed.

Gastroscopic examination showed a definite gastric ulcer in each of six patients in whom the roentgen-ray examination of the stomach was negative. Each of these patients improved on ulcer therapy and was discharged from the hospital. On the other hand in five cases with positive roentgen-ray evidence of ulcer gastroscopy was negative in four and gave indefinite findings in one. Only one of these diagnoses was confirmed, and that by operation.

Gastritis. Fifty-one of the patients examined showed some form of gastritis. Sixty-six per cent were males and 34 per cent females. The youngest patient was 19, the oldest 68 and the average age 36 years.

The symptoms of which these patients complained most frequently were abdominal pain and loss of appetite. The pain was usually epigastric. In seven instances it occurred immediately after eating and in 24 one to two hours after eating. Belching was the next most common symptom, then fullness, nausea and vomiting. Vomiting was infrequent.

In 47 per cent of the patients with gastritis there was no apparent associated lesion of the stomach, nor of any contiguous structures. The roentgen-ray examinations in these cases revealed no abnormality of the stomach. In the remaining 53 per cent associated lesions such as cancer, gastric, stomal or duodenal ulcer, and gall-bladder disease were present. All of these lesions were seen roentgenologically but the accompanying gastritis was not diagnosed.

The majority of writers feel that gastroscopy is the best method of diagnosing gastritis and many of them agree with Gaiter and Borland [5] who state that it is the only means by which a definite diagnosis can be made.

In our series of cases the fractional gastric analysis showed that hyperacidity and hypoacidity occurred with about equal frequency but were found only about half as often as a normal curve. About 14 per cent of the patients in this group had no free hydrochloric acid in the stomach contents and occult blood was found in over 50 per cent of the specimens.

The great variation in the interpretation of gastric analysis findings is emphasized by the studies of Henning.[6] The gastric analysis curves in a series of patients reported by him, and definitely diagnosed gastroscopically as having gastritis, showed 21 per cent with a normal curve, 11 per cent with

hyperacidity, 32 per cent with hypoacidity, 21 per cent with anacidity and 15 per cent refractory to histamine. Boros [7] states that gastric analysis is not an index to inflammation of the stomach.

Polypi. A benign polyp of the stomach was diagnosed by gastroscopy in six patients, of which four were male and two female. The youngest was 15, the oldest 56, and the average age 53 years. On one of these patients no roentgen-ray was made, polyp was suspected in two, cancer in two others, and in one patient the stomach was considered negative. However, subsequent operation and histological section proved both cases in which cancer was suspected to be benign polyp.

The superiority of gastroscopy in diagnosing benign tumors of the stomach, as shown in this group of patients, has been reported by Schindler, Gutzeit and Teitge on many occasions.

The symptoms of which these patients complained included epigastric pain, nausea, vomiting, anorexia, diarrhea and loss of weight. However, there was no one symptom common to all patients. A gastric analysis was performed on two of these patients. In both instances occult blood was present. The curve was normal in one case and showed no free hydrochloric acid in the other.

Summary

Of the 200 patients examined by both roentgen-ray and the gastroscope a lesion of the stomach was found in 128 cases. If we include the patients having gastritis we find that the roentgenological and gastroscopic diagnoses were the same in 62 per cent of all the cases. However, since the diagnosis of gastritis was not made in a single instance by roentgen-ray it might be a truer comparison of the value of the two methods of examination in identifying organic disease to omit these cases. When this is done the same diagnoses have been made by gastroscopic and roentgen-ray examination in 87 per cent of all the cases. The diagnoses of lesions of the stomach were made by roentgen-ray in 10 cases where the gastroscopic evidence was negative, whereas the diagnosis was made by gastroscopy in 15 patients when the roentgen-ray evidence was negative.

Of the 42 cases of gastric cancer 34 were diagnosed by both methods, 5 by roentgen-ray and not by gastroscopy and 3 by gastroscopy and not by roentgen-ray.

Of the 29 patients having gastric ulcer 18 were diagnosed by both methods, 5 by roentgen-ray and not by gastroscopy and 6 by gastroscopy and not by roentgen-ray.

Of the 6 patients having polyps of the stomach one was diagnosed by both methods, 5 by gastroscopy alone and none by roentgen-ray alone.

Total Patients Examined	200
Total Patients with Gastric Lesion	128
Total Patients without Gastric Lesion	72

No. Cases	Diagnosis	Made by Both Methods	Roentgen-Ray Alone	Gastroscopy Alone
42	Cancer	34	5	3
29	Ulcer	18	5	6
51	Gastritis	0	0	51
6	Polyp	1	0	5
72	Negative	71	0	1
200		124	10	66

Conclusions

1. The histories of the majority of the patients were so similar that special examinations of the stomach were required to make a differential diagnosis.

2. Roentgen-ray and gastroscopy are the most valuable methods of examining the stomach.

3. In none of the patients were we able to make the diagnosis by the gastric analysis alone. However, in a certain proportion of instances this examination was of significant help.

4. Gastroscopy has been shown to be a safe diagnostic procedure.

5. Gastroscopy can be employed simply and easily.

6. The value of gastroscopy is demonstrated by the fact that it is the most definite method whereby the diagnosis of gastritis and benign tumors can be made. Furthermore, in cases of ulcer or malignancy of the stomach gastroscopy is a definite adjunct to roentgen-ray examination.

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VITAMINS IN PEPTIC ULCER*

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Peptic ulcers have been produced experimentally in animals by deficiencies in vitamins B_1 and C.[1, 2] Those were severe deficiencies and we do not have evidence that such deficiencies are usually important in the etiology of peptic ulcers in man. The possible significance of vitamins in the treatment of peptic ulcers, however, deserves serious consideration. Some conclusions, which we are to present, must be considered tentative because they are based, in part, on indirect evidence.

Vitamin C may be important in respect to the process of healing of an ulcer or in respect to its tendency to bleed. In regard to the former we do not have direct evidence. The relationship of ascorbic acid to collagen formation in experimental deficiency [3] and in human scurvy [4] and its consequent relationship to wound healing [5] have been well demonstrated. It might be suspected, therefore, that vitamin C nutrition may be a factor in the healing of a peptic ulcer.

Chemical evidence of suboptimal vitamin C nutrition has been found to occur with remarkable frequency. It has been particularly frequent among peptic ulcer patients. People with abdominal symptoms are apt to avoid fruits and green vegetables. Croft and Snorf [6] found, among their first 100 determinations of blood ascorbic acid on private patients, 38 below 0.40 mg. per cent. Of these, 15 (40 per cent) had active peptic ulcers and 13 had had recent gastrointestinal hemorrhage.

Chemical evidence of vitamin C deficiency in a large proportion of peptic ulcer patients has been reported by Harris, Abbasy and Yudkin,[7] Archer and Graham,[8] Ingalls and Warren,[9] Lazarus,[10] Portnoy and Wilkinson,[11] Roux,[12] and Rao.[13] These series have been small, with the exception of one, which included 56 patients, but the finding has been constant.

Our experience is in accord with these findings. Thirty-nine of 58 patients with peptic ulcer had plasma ascorbic acid values below 0.5 mg. per cent, the beginning scurvy level of Farmer and Abt.[14] Two of the 8 patients who had values above 0.7 mg. per cent had received supplements of synthetic ascorbic acid.

As to the relationship between vitamin C nutrition and bleeding, the findings of Croft and Snorf [6] have been quoted above. Portnoy and Wilkinson [11] reported a mean plasma ascorbic acid of 0.34 mg. per cent among 31

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TABLE I

Plasma Ascorbic Acid in Peptic Ulcer Patients †

Plasma Ascorbic Acid—Mg. %	Number of Patients	Patients with Hemorrhage
0.20–0.29	10	3
0.30–0.39	15	7
0.40–0.49	14	1
0.50–0.59	8	0
0.60–0.69	3	0
0.7 –more	8*	1
Total Cases	58	12

* Two of these patients had received supplements of ascorbic acid.
† We are indebted for some of these analyses to Dr. J. G. Ruth and Dr. W. D. Block.

patients admitted for hemorrhage, contrasted with a mean plasma ascorbic acid of 0.42 mg. per cent among 25 patients with proved ulcers, without hemorrhage. Twelve of our 58 patients were bleeding at the time of admission, or while in the hospital. This incidence is about four times that of bleeding among other ulcer patients in this hospital during the same period. This was not a consecutive series, but the fact that ulcer patients with hemorrhage were more apt to have determinations of their plasma ascorbic acid done, adds to the significance of the figures. Ten of the 12 that bled were among the 25 who had plasma ascorbic acid values below 0.40 mg. per cent. It is probably of significance that two patients in this group had their hemorrhages after they had been in the hospital on an ulcer regime for 18 and 26 days respectively. Their plasma ascorbic acid values were 0.30 and 0.25 mg. per cent, respectively. One of these patients was found at autopsy to have an erosion into a large artery. One wonders if the treatment in these two cases would have been more effective if the deficiency in ascorbic acid had been remedied.

Two patients who were included in this group because of hematemeses despite negative roentgen-ray findings after the bleeding had ceased probably do not belong here. They had clinical scurvy evidenced by gingivitis and subcutaneous bleeding. One had subcutaneous bleeding only on capillary fragility test. The other lacked gingivitis but had spontaneous subcutaneous bleeding. Another patient with hematemesis and melena was not included because no ulcer could be demonstrated at autopsy. He did have subserosal and other hemorrhages and the plasma ascorbic acid of his heart's blood was 0.34 mg. per cent. He was edentulous and had no subcutaneous bleeding. It seems probable that in a certain proportion of cases, gastrointestinal hemorrhage, for which no cause can be found when roentgen-ray examination is feasible, is due to scurvy rather than to acute peptic ulcer.

Other than a scorbutic type of bleeding, hemorrhage from a peptic ulcer may be regarded as the result of an unfavorable balance between erosion and reparative processes. If a vitamin C deficiency impairs the healing process it might be expected to promote the occurrence of bleeding. Al-

though not proved, it is possible that such an effect on healing may be the explanation of (1) the high frequency of bleeding among those ulcer patients with plasma ascorbic acid values below 0.4 mg. per cent, (2) the infrequency of bleeding among those with higher ascorbic acid values, and (3) the occurrence of hemorrhage after considerable periods of the usual medical treatment in this hospital in two patients with plasma ascorbic acid values of 0.30 and 0.25 mg. per cent. As noted above, the bleeding in one of these was found to be from a large artery at the base of the ulcer. The relationship between vitamin C deficiency and bleeding may not remain as close in a larger series. The findings in these 58 cases, however, seem to make correction of any such deficiency indicated as part of the treatment of peptic ulcer.

Not only do ulcer patients commonly start treatment with a suboptimal vitamin C nutrition. Most ulcer diets are very deficient in that vitamin and the amounts of it required for saturation in patients receiving alkali therapy are greater than for normal individuals. Van Eckelen [15] and Heinemann [16] reported that the amount of ascorbic acid required to maintain saturation in normals was about 0.84 mg. per kilo per day (weight corrected to height). Heinemann [17] reported that four ulcer patients required an average of 1.25 mg. per kilo per day, and Warren, Pijoan and Emery [18] reported that 5 ulcer patients required an average of 1.05 mg. per kilo per day for saturation with ascorbic acid.

From 1 to 3 grams (occasionally more) of ascorbic acid are usually required to correct a significant deficiency. Two grams of ascorbic acid would be furnished by 4000 c.c. of orange juice. It seems preferable, at the beginning of ulcer treatment, to attain normal vitamin C nutrition quickly by giving moderately large doses, perhaps 200 mg., four times a day, until the plasma ascorbic acid is 0.9 mg. per cent or higher. If facilities for determination of ascorbic acid are not available and the anti-scorbutic quality of the previous diet is at all doubtful, it can do no harm to give, empirically, 2 grams of ascorbic acid in such divided doses. Thereafter, 100 c.c. of orange juice or 50 mg. of ascorbic acid may be given daily until enough other fruits and vegetables are added to the diet to make it adequate.

Other vitamins may be of importance in the treatment of peptic ulcer. We have had a few patients on an ulcer diet for a long time, taking less than the allowed amount of meat and vegetables, who have developed pellagrous symptoms. Some have had the chronic skin changes that we have described; [19] some have had glossitis; a few without objective evidence of pellagra have had abdominal symptoms, other than ulcer pain, relieved following the administration of nicotinic acid. Wheeler and Sebrell [20] reported that milk was only a fair pellagra-preventing food. Three of 5 dogs receiving 15 c.c. of evaporated milk per kilo (equivalent to 2 quarts of milk a day for a 70 kilo man) developed blacktongue.

—Vitamin B_1, like ascorbic acid, is easily destroyed in an alkaline medium. We have not found a significant amount of it to be destroyed when incubated with gastric juice at any physiological pH. We have found that as much

as 56 per cent of thiamine, incubated with bile or pancreatic juice at their natural pH may be destroyed.[21] Also, there is a considerable adsorption of thiamine when it is exposed in vitro, to some anti-acids in gastric juice. We have not determined exactly how much of the absorbed thiamine may be recovered by the body but judge from our findings that a major portion of it is recovered.

The Sippy regime, with its hourly milk and cream, contains a good amount of thiamine. Nevertheless, we have found that, during the third week on that regime, 19 of 20 patients had a urinary excretion of thiamine in the range of patients with a definitely deficient intake.[22] Eleven of 17, however, excreted a normal fraction of a 5 mg. test dose of thiamine given with a meal. The low excretion before, and the normal excretion after the test dose are findings obtained after a short period of experimental thiamine deficiency, indicating that the body stores of the vitamin are not seriously depleted. Thiamine deficiency, as well as alkalosis, may be a cause of anorexia in ulcer patients receiving intensive alkali therapy, and might become of greater importance if such treatment were continued over a long period. We have not found positive chemical evidence of thiamine deficiency in patients on six meal ulcer diets with less than hourly doses of alkalies.

The destruction of thiamine in bile and pancreatic juice, the alkalinity of which is unmodified by stomach acid, is possibly of more significance in another situation. Patients with achlorhydria require a larger intake of thiamine than do subjects with a normal gastric acidity. Consequently, as we have found,[22] they are apt to show chemical evidence of thiamine deficiency. It is suggested that this may be an explanation of the cord changes in pernicious anemia.

Summary and Conclusions

The majority of patients with peptic ulcer studied have a deficiency in vitamin C.

The pathology of vitamin C deficiency is such that it might be suspected to have a deleterious effect on the healing of a peptic ulcer.

The correlation between low plasma ascorbic acid and the occurrence of hemorrhage in peptic ulcer is suggestive evidence of such an impairment of healing.

Some patients considered to have had an acute peptic ulcer, and with negative roentgen-ray findings after bleeding had ceased, probably had a scorbutic bleeding.

It seems indicated, in the treatment of peptic ulcer, to correct promptly any vitamin C deficiency.

Ulcer patients may develop a pellagrous type of deficiency if they continue to restrict meat and green vegetables.

Ulcer patients receiving intensive alkali therapy show chemical evidence of a deficiency in vitamin B_1. A large proportion of thiamine incubated with bile and pancreatic juice at their natural pH is destroyed in vitro.

This has not been found to be important for ulcer patients who do not continue intensive alkali therapy for long periods. Such destruction of thiamine may be the cause of combined system degeneration.

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PREVENTION OF PERNICIOUS ANEMIA: RECOGNITION OF THE LATENT STAGE IN RELATIVES *

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THE diagnosis of Addisonian pernicious anemia ordinarily is made over a year after symptoms have been definitely established.[1] About 75 per cent of patients with this disease have involvement of the nervous system,[2, 3] and this condition is often recognized too late to prevent partially disabling nervous system lesions. The deaths attributable to pernicious anemia are due largely to complications of these lesions. Treatment may prevent further progress but cannot correct irreparable spinal cord damage.

The challenge for the future must be to diagnose pernicious anemia before the appearance of blood and nervous system changes. This will inaugurate an era of prophylaxis in pernicious anemia.

We wish to review the accumulating evidence that the potential cases of the disease are in the relatives and to suggest a scheme by which they may be recognized in the latent stage.

HEREDITY AND PERNICIOUS ANEMIA

Hereditary predisposition is becoming more and more generally accepted although it often is difficult to prove in an isolated instance. To establish heredity as an etiological factor in a human disease such as Addisonian pernicious anemia, which is relatively rare and tends to appear late in life, is difficult.[4, 5]

Where accurate family histories are impossible to obtain for several generations the pedigree method is unreliable. The number of living parents available for study is small. The determination of an increased frequency of consanguineous marriages in parents, which would suggest a recessive type of inheritance, is difficult. The demonstration that the disease occurs more frequently in two members of a family than can be accounted for by chance alone is, however, good statistical evidence.

The most conclusive data are those obtainable from the study of twins. Hereditary diseases must show an invariable occurrence in both uniovular twins, if one has the disease.

FAMILY INCIDENCE

Despite the difficulties incident to the pedigree method, pernicious anemia has been found in several members of families to an extent far above the expectation from chance alone. The grouping in certain families is so marked that the genetic factor cannot be questioned.

* Read at the Cleveland meeting of the American College of Physicians April 2, 1940.
From the Department of Medicine, University of Southern California School of Medicine.

There are 235 instances of multiple familial occurrence. Conner [6] cited 110 in 1931; 105 have been found in the literature since then; and I have added 20 more families, in 18 of which the proof is definite (tables 1 and 2).

TABLE I

Families in Which Two or More Members Have Pernicious Anemia

Authors	Number of Families	Relatives Involved			
		Siblings	Two Direct Generations	Patient and Aunt or Uncle	More Distant or not Stated
62 *	215	41	48	4	122
Personally collected	20	9	9	2	—
Total	235	50	57	6	122

* Bibliography, 6 to 32 inclusive.

The data in many individual families supply convincing evidence as to the hereditary pattern. Consanguineous marriages are of particular value in that they should make recessive traits manifest (chart 1).

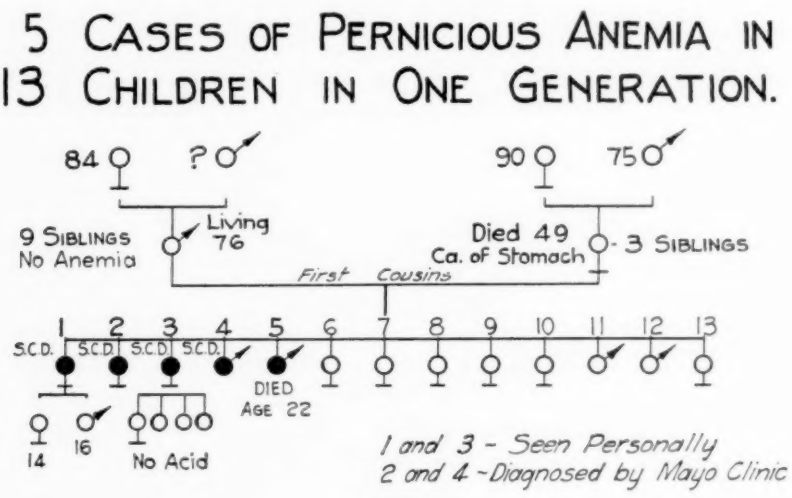

CHART I

Family J of our group is interesting. Two first cousins, whose parents lived to old age, married and had 13 children, of whom five had pernicious anemia (four proved). Two of these children, sisters, I personally have observed, both of whom showed a macrocytic hyperchromic anemia, anacidity after histamine and subjective and objective signs of spinal cord degeneration. Another sister died at the Mayo Clinic on October 19, 1917, diagnosed as pernicious anemia. A brother was seen at the Mayo Clinic

on October 14, 1936, and diagnosed pernicious anemia, with subacute combined cord degeneration. The other brother, by hearsay, was said to have died at the age of 22 of pernicious anemia.

TABLE II

Pernicious Anemia in Several Members of a Family
(Since Conner, 1930)

	Families	Relationship
Moschcowitz, F.	1	"Five members in three generations."
Hartfall and Witts	1	Patient, sister and two maternal aunts.
Ridder	1	Patient, sister, and maternal aunt.
Liepelt	1	Mother and daughter.
Frank	1	Identical twins.
Winternitz	2	(1) Three brothers. (2) Father and son.
Ungley and Suzman	1	Brother and sister.
Dobriner and Rhoads	1	Father and son.
Wilkinson and Brockbank	14	(1) 4 siblings. (2) 9 times in two or more generations. (3) Once—patient and aunt.
Piney	1	Patient and father.
Krantz	1	Patient and mother.
Beebe and Wintrobe	1	Patient and mother.
Ellis (Quoted by Hurst)	1	Identical twins.
Strandell	3	(1) Mother and son. (2) Brother and sister. (3) Identical twin sisters.
Heath	1	Two sisters and brother.
Scheidel (Cited by Ridder)	1	Patient and sister.
Horsters and Krohn (Cited by Ridder)	2	"Two families."
McGhie	1	Daughter, father and mother.
Finney	1	"Patient and relative."
Murphy	40	"Two or more members."
Kaufmann and Thiessen	8	(1) 4 siblings. (2) Mother and son (twice). (3) Cousins. (4) Identical twins.
Schemm	6	(1) 5 siblings. (2) Mother and son.
Weitz	10	"Through three generations."
Bremer (Cited by Weitz)	1	7 cases in three generations, including two feminine twins.
Naegeli	3	(1) Mother and daughter. (2) Four relatives. (3) Father and son.
Michaud (Cited by Askanazy)	1	Father and son.
Askey*	20	(1) 9 siblings. (2) 9 in two generations. (3) Patient and uncle. Patient and nephew.
Total	125	

* I wish to thank members of the Section of Internal Medicine of the Los Angeles County Medical Association for permission to report 10 of these families.

Since this paper was written, I have discovered another family, daughter aged 43, and mother aged 82, with definite cord damage in both; also another report of a boy, 18, and his mother, 48, with pernicious anemia, by Wilkinson, J. N., *in* Clin. Va. Mason Hosp., 1939, xviii, 19.

STUDY OF IDENTICAL TWINS

Studies of identical twins, one of whom had pernicious anemia, have been reported in eight pairs (table 3).[11, 19, 30, 27, 33, 20, 34] In four pairs the

TABLE III

Pernicious Anemia in Twins

Author	No.	Uniovular	Sex	Age
Frank	1	Yes	M.	57—Both developed pernicious anemia within 1½ years. Both had Towerskulls, both developed paralysis agitans, both high grade morons (mental age 8).
Ellis (Cited by Hurst)	2	Yes		Both proved (details unobtainable).
Bremer (Cited by Weitz)	3	Not stated (probable)	F.	Both proved (details unobtainable).
Kaufmann and Thiessen	4	Yes	F.	55—Developed pernicious anemia within 8 years. One first to develop it always in poorer health. Both diabetics.
	5	Yes	F.	68—One pernicious anemia. Other normal blood smear but no blood count done, no gastric analysis. Had hypersegmentation of leukocytes.
Werner	6	Yes	M.	57—One pernicious anemia. Other—"anacidity." Since brother developed pernicious anemia has eaten liver, preventing later recognition.
Strandell	7	Yes	F.	68—Died with cord involvement. Other "achylia," numbness in one foot, no anemia. Considered incipient anemia.
Dedichen	8	"Resembled each other"	F.	86—One "pernicious-like anemia" with "achylia" test not stated. Other had "pernicious-like anemia" with free acid.

disease has appeared in both members; in three, it is probably latent in the second member. In one pair, aged 86, although there is anemia in both, the second member has free acid present. The data in this last instance are so meagre that the diagnosis can well be questioned in both twins.

This is strong evidence for heredity as an etiological factor in these instances, but control studies of dizygotic twins should be made.

ANACIDITY IN RELATIVES

Increased frequency of pernicious anemia among relatives should be reflected in an increased incidence of its precursor, anacidity.

All the studies of relatives analyzed as to age and the nearness of blood relationship show an increased incidence of anacidity, particularly in the two decades prior to 40, and about a double percentage of anacidity among the near relatives as opposed to distant relatives (tables 4, 5, 6, 7).[27, 33, 6]

ANACIDITY PRECEDING PERNICIOUS ANEMIA

Test meal anacidity has been found to precede pernicious anemia for from 2 to 30 years in 57 of 60 patients (table 8).[20, 35] These 60 cases were obtained by selecting from a group of 1061 patients previously studied those with previous gastric analyses.

Individual case reports of anacidity preceding pernicious anemia by many years have been collected. It has been found that of a total of 174 cases in

TABLE IV

Achlorhydria in Near Relatives (Siblings, Children, Parents) and in Distant Relatives (Test Meal)

	No.	No. with Anacidity	Per Cent
Near Relatives			
Conner	147	37	25
Kaufmann and Thiessen	123	31	17.1
Werner *	—	—	19
Distant Relatives			
Kaufmann and Thiessen	32	3	9.4
Werner *	—	—	9

* Of 525 tested, 19 per cent of near relatives had anacidity, 9 per cent of distant relatives. The number in each group was not given.

TABLE V

Achlorhydria in Relatives (Test Meals)

A compilation of all tests not classified as to age groups.

	Number Examined	No. with Anacidity	Percentage
Conner	154	40	25.9
Neuburger	29	1	3.4
Weinberg	24	10	41.7
Zadek	46	10	21.7
Wilkinson and Brockbank	38	9	23.7
Dorst	6	2	33.3
Queckenstedt	4	1	25
Kaufmann and Thiessen	167	26	15
Werner	525	58	11
Martius	4	3	75
Totals	997	160	16

TABLE VI

Percentage of Incidence of Anacidity in Various Decades of Life (Test Meal) of Relatives

	Per Cent of Anacidity		
Age (Years)	Normals (5204) (Bloomfield and Polland)	Near Relatives (141) (Kaufmann and Thiessen)	Near Relatives (141) (Conner)
20–29	5.3	17	13.5
30–39	9.5	16	20
40–49	16.7	15	46
50–59	24	31	29
60–plus	35.4	29	50

The most significant finding is the agreement on a definite increased incidence in the 20–40 age period. Conner found an increased incidence in all ages.

TABLE VII

Percentage of Incidence of Anacidity in Relatives in Various Decades of Life
(Histamine)

Age (Years)	No. of Subjects	No. with Anacidity	Per Cent Anacidity	Per Cent Anacidity 654 Normals (Polland)
0–20	5	1	20	0
20–29	14	1	7.1	3.5
30–39	22	5	22.7	5.2
40–49	12	1	8.3	14.3
50 plus	8	2	25	20.6
	61	10	16.3	12

This shows an increased incidence prior to 40. This may be due to those with the early developed anacidity of potential pernicious anemia. Only analysis of a large group of histamine anacid relatives can determine if the increased incidence of anacidity in all ages is due to increased incidence before 40.

TABLE VIII

Achlorhydria Preceding Pernicious Anemia
(Test Meals)

Representing study of group including all preceding gastric analyses.

	Group	No. with Preceding Gastric Analyses	No. with Anacidity
Strandell	117	21	20
Rozendaal	906	36	34
Personal cases	38	3	3
Totals	1061	60	57

which previous gastric analyses had been recorded 171 had shown anacidity (table 9).

TABLE IX

Achlorhydria Preceding Pernicious Anemia, Including All Reported Cases (Test Meals)

	No. of Group Studied	No. with Preceding Gastric Analyses	No. with Anacidity	No. of Authors
Ivy, Morgan and Farrell*	?	34	34	20
Murphy, W. P.	(1)			
Schemm, F. R.	(2)	3	3	2
Meulengracht	368	77	77	1
Strandell	117	21	20	1
Rozendaal	906	36	34	1
Askey	38	3	3	1
Totals		174	171	26

* Their 36 reported cases include two by Conner, which are probably duplicated by Rozendaal.

Potential Cases of Pernicious Anemia

Save in negligibly rare cases, true anacidity is always found in pernicious anemia and must necessarily precede its development. Those relatives with a pernicious anemia genotype should show histamine refractory anacidity for a variable period prior to manifestation of the anemia itself. The finding of anacidity justifies at least the suspicion of potential pernicious anemia. The presence of free acid indicates that there is little immediate risk of its development.

The Hazard of True Achlorhydria in Relatives

Anacidity in an ordinary individual represents a negligible hazard as regards the risk of later development of pernicious anemia. Bloomfield [39] says the risk is one in three or four hundred. No statistical data are available to measure the hazard of achlorhydria in relatives of pernicious anemia patients. What percentage are prepernicious anacidities cannot be stated.

Until a practical test is devised to interpret the anacidity in terms of deficiency of Castle's intrinsic factor, we will have to base our prognosis upon studies which indicate the number of anacid relatives who later develop the disease. Only observations of large numbers over a long period of time can furnish dependable data of this nature.

It will probably be found that in such a study of the relatives of a case of pernicious anemia, those found to have anacidity will prove eventually to comprise most if not all of those who develop pernicious anemia. This should be especially true when the group studied falls in the age group of the fifth and sixth decades.

Close observation of such a large group would not only establish the comparative hazard of true anacidity in the relative but would lead to an early presumptive diagnosis before development of marked blood and nerve changes. This would constitute a definite step toward the prevention of pernicious anemia.

Study of Pernicious Anemia Families

In the last six years we have adopted a tentative scheme for the study of families in which pernicious anemia was present.

We arbitrarily have accepted heredity as the most important etiological factor, and thus justified our consideration of the family as the unit of greatest potential concentration.

We have attempted to locate manifest pernicious anemia in other family members by detailed histories, personal investigations and correspondence with the attending physicians.

Ten families were discovered with two or more having the disease, and 10 were collected from fellow internists in Los Angeles. In 18 of these 20 families the familial occurrence was proved, in two it was based on hearsay.

Study of Families

To discover *latent* pernicious anemia, we have considered every relative as a potential case until disproved. We have told every patient of the familial nature of the disease, and have requested each to have his relatives come in for a histamine gastric analysis. Many relatives refused, but 61 agreed to this study, of whom 10 showed anacidity. The 51 with acid were arbitrarily considered as in no imminent danger, and the 10 with anacidity were considered as potential cases who, in later years, might develop the disease. The assumption of anacidity based on a single histamine study we realize is again arbitrary, but is necessary due to the difficulty of getting even a single test in normal relatives.

To avoid any phobia which might lead to premature eating of liver and the prevention of early recognition, they were not told the early symptoms.

In the families thus studied the following developments have occurred: Two relatives who refused gastric analyses have developed severe crippling pernicious anemia. Of the 10 anacid relatives, four have developed signs or symptoms of early pernicious anemia; two have developed hypochromic anemia, apparently idiopathic. Three have normal blood, and one cannot be located.

Prevention of Pernicious Anemia

The following cases we believe are significant:

I. Two individuals, because of pernicious anemia in the family, were considered possible potential cases of the disease. They were both in good health and refused gastric analysis. In two and five years respectively they developed pernicious anemia with marked spinal cord damage. Despite treatment one is totally disabled and one is partially disabled.

It is highly probable that if they had allowed gastric analyses, true anacidity would have been found, and they would have been watched for early symptoms.

Case Reports

Family 1. Mrs. M.D., aged 69 years, has been under treatment for pernicious anemia since June, 1935. A gastric analysis on her daughter done in 1936 showed hypoacidity. The son, aged 48 years, was in good health in 1936 and refused a gastric analysis. In May, 1938, Dr. Robert W. Langley saw him with an attack of severe precordial pain. The electrocardiogram failed to show coronary occlusion. The blood count showed 1.7 million erythrocytes, 40 per cent hemoglobin (Sahli), and a typical blood smear of pernicious anemia. There were diminished patellar reflexes, dysmetria in the heel to knee test, diminished vibratory sense and impaired sense of position. There was marked instability in walking. There was no free hydrochloric acid after histamine stimulation. His response to liver therapy given parenterally was typical. In March, 1939, his erythrocytes were 4.3 million and his hemoglobin (Sahli) 80 per cent. He is now totally disabled. Although able to walk without a cane, he is ataxic and mentally "has lost his grip." Formerly a high business executive, he now can transact little business.

Family 2. Mr. D. S., aged 65 years, has been under treatment for pernicious anemia since 1926, when his life was saved by the discovery of liver therapy. His sister came to ask about him in 1934. At that time she was in good health but was asked to have a gastric analysis done, which she refused. In February, 1939, Mr. D. S. mentioned that his sister, now aged 70, living in a neighboring city, was unable to walk because of "arthritis," and that she had a "peculiar anemia, but not pernicious anemia." She was seen and found to have diminished reflexes, diminished senses of vibration and position. She was unable to walk without holding on to a chair. She had been on oral liver and iron capsules and her count was 3.9 million erythrocytes, 80 per cent hemoglobin (Sahli), 6,200 leukocytes with slight macrocytosis in the blood smear. She was given liver parenterally; 20 c.c. reticulogen (Lilly) over a period of three weeks. In six weeks she had improved so that she could walk without a cane. At the present time her blood count is normal, but she is handicapped by ataxia.

11. Two anacid relatives, one and two years after histamine study, developed early symptoms of pernicious anemia and were relieved by liver treatment.

Case Reports

Patient 1. Mrs. L. C., aged 42 years, was first seen in 1933 with laryngitis. She said her uncle had died of pernicious anemia. This was proved by a letter from the attending physician. Two aunts were also said to have died of pernicious anemia, but this was not verified. She was in general good health. In 1936 a blood count showed 4.9 million erythrocytes, 9,000 leukocytes; 81 per cent hemoglobin (Sahli), with a normal differential count and blood smear. The gastric analysis after histamine showed true anacidity. Two years later, in July, 1938, she complained of malaise and "beginning arthritis" saying that her hands tingled and her feet felt numb. She had had a sore tongue for several months, which had puzzled her husband, a dentist, since gingival sepsis was absent. The tongue was clean and smooth at the edges. There was no disturbance of sense of vibration or of muscle position. The reflexes were normal. A blood count showed 3.62 million erythrocytes; 10.6 hemoglobin (Sahli). She was leaving for a motor trip to Seattle the next day. An intramuscular injection of 4 c.c. reticulogen (Lilly) was given as a therapeutic test. She returned on September 12, 1938. Her sore tongue and paresthesia had gone. Her blood count showed 4.03 million erythrocytes; 70 per cent hemoglobin (Sahli). Liver injections at intervals have been given and she has had no return of symptoms. In 1940, although having no glossitis or paresthesia a blood study showed definite macrocytosis.

Patient 2. Mrs. W. E., aged 50 years, was first seen in September 1937, with Dr. C. G. Toland. She had a moderately toxic diffuse goiter. Her mother had died of pernicious anemia. In 1935 she had been found to have no acid by test meal. We repeated the gastric analysis with histamine and found true anacidity. Her blood count was 4.39 million erythrocytes; 74 per cent hemoglobin (Sahli); 7,400 leukocytes, with a normal blood smear. A subtotal thyroidectomy was done on January 10, 1938, from which she recovered satisfactorily. In July, 1938, she developed numbness in both feet and a sore, burning tongue, for the latter of which she consulted her dentist. He said she was a little pale, and as a coincidence, because his mother had pernicious anemia and took liver, and her mother had had pernicious anemia, advised her to take some liver capsules. She took them regularly and in February, 1939, when next seen, her paresthesia and glossitis had gone. Her blood count showed 4.78 million erythrocytes; 78 per cent hemoglobin (Sahli); 7,200 leukocytes and a normal blood smear. She has refused to stop liver because of the marked improvement.

III. Two other anacid relatives, aged 64 and 62, show slight anemia, but the most significant changes are those of macrocytosis in the blood smear, confirmed by definite increased mean cell volume, and color and volume indexes over one (table 10).

Davies and Illyd-James [40] found only one in 14 normal people over the age of 60, with true anacidity, with a color index over one. In adults, age has no effect on the size of the red blood cells. Both of these relatives are in poor health, one with slight impairment of vibratory sensation and a smooth tongue.

IV. Two anacid relatives apparently have developed an idiopathic hypochromic anemia. It has not been proved that there is not latent or coexistent pernicious anemia.

Case Reports

Case 1. Mrs. R. G., aged 43, showed true anacidity after histamine January 28, 1935. Her mother was under treatment for pernicious anemia with marked cord involvement. She was in good health and consented to a stomach analysis only after considerable persuasion. A blood count then recorded showed hemoglobin 12.9 grams, erythrocytes 4.10 million (color index 1.09), leukocytes 6,555, with slight variation in size and shape of the red cells. She moved away from town soon afterward and for several years attempts to locate her failed. March 1, 1940, she was located in a distant town and gave the following history: About 1937 she developed some tingling in her hands and some transient soreness of her tongue. Remembering that her mother had had similar symptoms and that I had emphasized the familial nature of the disease, she took various liver and iron preparations which her husband, a druggist, suggested. She still lost weight and developed severe headaches.

In February, 1939, her blood count showed erythrocytes 3.68 million, and hemoglobin (Newcomer) 71 per cent.* From February to May, 1939, she took oral liver but in May the hemoglobin was 59 per cent and the erythrocytes 3.8 million. She was then given large doses of iron supplemented by copper.

On February 16, 1940, her hemoglobin was 83 per cent and erythrocytes 3.97 million. She has gained eight pounds and her headaches are better. There was at no time any reason to explain the anemia upon the basis of blood loss.

The interpretation of this case is difficult. Her response to oral iron and not to oral liver would suggest a hypochromic anemia. The possibility that there is an iron deficiency anemia in combination with pernicious anemia must not be ignored. Without determining the response to parenteral liver to be sure of adequate absorption, this cannot be stated.

There are many instances of idiopathic hypochromic anemia preceding development of pernicious anemia. There is good reason to believe they may coexist.[41] This case is at least significant in demonstrating an antecedent true anacidity four years before the discovery of an apparently idiopathic hypochromic anemia.

Case 2. Mrs. B. C., aged 23, whose mother, aunt, and two uncles had proved pernicious anemia (Family J) was seen January, 1938, with her sister. Both had

* Information obtained through courtesy of Dr. W. A. Richardson, Loma Linda, California.

Table 8
Analysis of Ten Anacid Relatives with Subsequent Blood Findings

TABLE X

Analysis of Ten Anacid Relatives with Subsequent Blood Findings

Case	Age	Sex	Date of Gastric Analysis	Blood Count	General Health	1938	1939	1940							Blood Smear	Remarks
								R.B.C. per Cubic mm.	Hemoglobin in gm. per 100 c.c.	Hematocrit per 100 c.c. Blood	Mean Cell Volume	Mean Cell Hemoglobin	Color Index	Volume Index		
1	19	F.	1935	Normal.*	Good.			4.1	12†	36‡	87	29.5	.87	.95	Normal	Excellent health.
2	38	F.	1935	Slight anemia. C.I.—1.17.	Good.		Hypochromic anemia. R.B.C. 3.8 mil. Hemoglobin 8.5 gm.	3.97	1.25	Not done.	—	31.4	1.08	—	—	Fair health. Improvement on iron, not to oral liver. Parenteral liver not given.
3	38	F.	1936	Normal.	Good.	Macrocytic anemia. Sore tongue, paresthesia. Relieved by liver.		4.16	13.5	40	96	32.4	1.13	1.06	Macrocytosis. Ovalocytosis. 5% 5 lobed neutrophiles. 2% 6 lobed neutrophiles.	Fair health. No return of glossitis or paresthesia. Inadequate liver indicated by macrocytosis.
4	64	F.	1936	Normal.	Fair. Easy fatigue.			3.69	12.2	36	97.5	33	1.13	1.08	Macrocytosis. No hypersegmentation.	Poor health. Easy fatigue. Tongue smooth. Impaired vibratory sense in left leg. No sore tongue or paresthesia.
5	48	F.	1937	Normal.	Toxic goiter.	Sore tongue, paresthesia. Relieved by liver.		Could not be obtained.								Cannot be located. One year ago feeling well on oral liver.
6	33	F.	1937	Normal.	Good.			4.49	13.3	38	86	29.6	.88	.92	Normal save for 9% 5 lobed neutrophiles.	Fair health; fatigues easily. "Nervous indigestion."
7	23	F.	1938	Normal.	Fair, easy fatigue. Helped by yeast.	Hypochromic anemia. Hemoglobin 8.2 gm. R.B.C. 4.99 million.		5.17	15.4	44	85.1	29.7	1.02	.98	Normal.	Has taken no iron since 1938. Fatigue and sore tongue; relieved by liver injections last two years.
8	38	M.	1938	Normal.	Good.			5.5	16.4	46	83	29.8	1.03	.93	Normal. 5% 5 lobed neutrophiles.	Excellent health.
9	37	M.	1938	Normal.	Good.			Not located.								Moved to North Carolina. Cannot be located.
10	62	M.	1939	Normal.	Good.			4.24	13.5	42	98.6	31.8	1.08	1.1	Macrocytosis. 6% 5 lobed neutrophiles.	Fair health. Is losing weight. Tires easily. No sore tongue or paresthesia.

* Normal means red cell count and hemoglobin normal. Packed red cells not determined.

† Hemoglobin determinations by Sahli-Hellige Hemoglobinometer save for (2) in which Newcomer Hemoglobinometer was used.

‡ Packed red cell volume determined by Sanford-Magath tubes. Centrifuge—3000 R.P.M. to constant volume.

histamine gastric analyses. Mrs. B. C. showed true anacidity; her sister had normal free acid. Mrs. B. C. gave a history of having had stomach trouble since the age of 18, characterized by generalized abdominal pain, nausea and vomiting. Attacks would last several hours and came every few nights; they were not apparently attributable to food or nervousness. Her periods had appeared at 14 and had been regular and not painful or profuse. In 1935 she had had a normal delivery. In 1936 her appendix had been removed with no improvement. In 1937 she started eating yeast cakes three times daily and after two months had no further stomach trouble although she had had trouble continuously for a year prior. Her blood count in January, 1938, showed 9.8 gm. hemoglobin, 5.2 million erythrocytes, 8,500 leukocytes.

In March, 1940, she was located in a neighboring city and gave the following history:

In May, 1938, she felt so weak she went to a health clinic. At that time her hemoglobin was 59 per cent (Newcomer), erythrocytes 4.99 million. The blood smear showed "severe anisocytosis and poikilocytosis, an occasional normoblast, many microcytes." She was given reduced iron capsules and liver injections (Lilly) two c.c. twice weekly. Despite the treatment her blood count October 13 was 61 per cent hemoglobin (Newcomer), 4.47 million erythrocytes. She was moving away and was given liver extract powder to take, and although her blood count did not rise abruptly she said the treatment "helped her immensely in every way." Her stomach trouble left, her appetite returned, her strength came back to normal. She moved to San Bernardino, and in January, 1939, began to tire again. She again was given liver injections by her sister, two a week for three months, and again gained normal strength. She took no iron capsules after August, 1938.

In January, 1940, she again had injections twice weekly for six weeks (Lilly's concentrated liver extract, 2 c.c.). These have relieved her nausea.

For the last two years she had complained of a raw, sore tongue which was relieved entirely by liver. She also said that when she was tired out her hands and feet felt as though "they were going to sleep." She had mentioned the tongue to her mother who had remarked that that had been one of her early symptoms.

March 18, 1940, one month after a six weeks' course of liver injections, her blood count showed hemoglobin 15.4 gm., erythrocytes 5.17 million, mean cell volume 85.1 cubic microns, mean cell hemoglobin 29.7 micrograms, color index 1.02, volume index .98.

She looks in good health. She says she always picks up a great deal after having liver. There are no abnormal neurological findings.

This case is unusual in that the blood picture was definitely hypochromic and should have responded to iron, and yet her improvement seemed to follow the use of liver.

Discussion

Over a six year period of observation, four of 10 histamine anacid relatives have developed apparent incipient pernicious anemia; two hypochromic anemia; three are in good health with normal blood; one cannot be located.

Early cases necessarily cannot be proved by criteria applicable to advanced cases. The four cases believed to be incipient pernicious anemia were proved to be macrocytic in three. In one the diagnosis was thought justifiable due to the clear-cut history of glossitis and paresthesias relieved by liver.

The development of hypochromic anemia in two cases stresses the tendency of the apparently idiopathic form to appear in pernicious anemia families. Whether there is latent or coexistent pernicious anemia can only be conjectured at present.

The significant feature is that 10 relatives were considered as having potential pernicious anemia while in good health. The appearance of early signs and symptoms in four out of 10 with the possibility of later development in others indicates that the hazard of achlorhydria in a relative is very high.

It suggests the importance of knowing whether a patient with achlorhydria has or has had pernicious anemia in the family.

Since pernicious anemia may occur only in a single generation, the patient may have no knowledge of a family occurrence. It would seem important, for the future, that patients be advised of this hereditary tendency, so that their grandchildren may be able to state positively of this occurrence, thereby placing achlorhydria in that family in the category where pernicious anemia may be suspected as a possible rather than an improbable development. Secondly, the physician should study the family rather than the patient alone. If the disease is familial, or hereditary, the families will contain latent cases.

Those relatives with free acid present could practically be eliminated, and the anacid relatives be watched for early signs and symptoms. It would appear unwise to acquaint them with the early symptoms as it would lead to the promiscuous use of liver and prevent the recognition of the early development.

It is certain that the insidious development of severe spinal cord damage may be prevented in many cases if the relatives of pernicious anemia patients are sought out and grouped by means of the histamine gastric analysis.

The physician's duty is to the family, not to the patient alone.

Macklin [25] has said "the ancestor, immediate or remote, constitutes the forgotten man in medicine." We should go by the rule that the blood relatives of patients with pernicious anemia are potential cases until proved differently.

Summary and Conclusions

1. Twenty families with two or more members having pernicious anemia have been added to the literature, making a total of 235 families.

2. The increased familial incidence and the available data regarding the disease in monozygotic twins suggest that pernicious anemia is frequently, if not invariably, transmitted by heredity.

3. The incidence of anacidity in relatives of pernicious anemia patients is increased over that in normal groups of the same age and sex. Anacidity is twice as high in near relatives as in distant relatives.

4. Sixty-one relatives were examined by histamine gastric analyses and 10 (16 per cent) found anacid. These were considered as potential cases.

5. Four of the 10 have developed incipient pernicious anemia. Two have developed idiopathic hypochromic anemia.

6. Two relatives who refused gastric analyses developed pernicious anemia with severe spinal cord damage.

7. The development of severe pernicious anemia and of its neurological sequelae can be prevented in many instances if all anacid relatives are considered as being potential cases of the disease.

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THE FUNCTION OF *LISTERELLA* IN INFECTION *

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WHEN Sir David Bruce discovered *"Micrococcus" melitensis* as the causative organism of Malta fever, there was little evidence to indicate that the future was to unfold a new group of human diseases tracing their origin to animal sources. Yet, as is also true of other bacterial and viral diseases, brucellosis has since become a well-recognized series of manifestations which aptly illustrate the precept that the animal may serve as a reservoir for the dissemination of disease to man. While it may be an imprudent, if not precarious, gesture to attempt prognostication, the contingency nevertheless seems not too remote that medicine may witness another example of a group of infections implanting themselves from animals into man. Thus, there is reason for contemplating that the bacterial genus *Listerella,* now occurring fairly ubiquitously among animals and fowls, is gradually adapting itself to man, with listerellosis becoming in time as common perhaps as brucellosis.

It is primarily with the intention of preparedness, when and if the time actually arrives, that the present communication is being made. Because of studies recently undertaken in this laboratory in this connection, it appears to be an opportune moment to introduce the subject for general discussion and thought. Reviewing, first, the bacteriological properties of the genus *Listerella,* as determined in this laboratory, it is then proposed to discuss briefly the chief characters of animal infection; to present a résumé of verified listerellosis in man; and, finally, to offer for consideration personally acquired evidence both sustaining and opposing the concept that infectious mononucleosis may be an expression of the same organism.

BACTERIOLOGY OF *LISTERELLA*

Listerella (*Bacterium monocytogenes*) was first discovered by Murray, Webb, and Swann[1] in 1926 as the incitant of a spontaneous infection in stock rabbits and guinea pigs. The infection was characterized by mononucleosis, occasional involvement of the mesenteric glands, with focal necrosis of the liver, and fatal termination. Since then, bacteriological studies have been made by other workers.[2] The organisms of this group may grow poorly, so that blood should be added routinely to media for enrichment. In the presence of blood, colonies are small and grayish and are surrounded by a zone of hemolysis. While the organism is a small gram-positive, motile rod, its arrangement together with its colonial appearance causes its confusion with hemolytic streptococcus or diphtheroids.

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In an effort to obtain more fundamental information on this group, 22 strains * have been collected from various sources, and a comparative study has been made in this laboratory. Cultures have been carried on blood infusion agar or in infusion broth to which was added 5 per cent ascitic fluid and 0.03 per cent dextrose. Almost as good growth, however, may be obtained in tryptose broth (2 per cent tryptose, 0.5 per cent sodium chloride, 0.03 per cent dextrose, and 1000 c.c. water, pH 7.4–7.6). It is interesting in this connection that the strains from ruminant animals appear to grow most heavily, in some cases even profusely.

A study of the reactions in different media revealed no test of diagnostic possibilities. Thus, in sugar media, all strains caused fermentation without gas of dextrose, maltose, salicin, levulose, mannose, rhamnose, and sucrose, while in lactose there was only a trace of acid. No effect was exerted on mannite, sorbite, inosite, arabinose, xylose, adonite, raffinose, inulin, dulcite, and galactose. Other differential tests, as production of hydrogen sulphide, ammonia, creatinine, indol, nitrates, nitrites, and Voges-Proskauer reaction were all negative. In litmus milk there was slight acid formation with decolorization of litmus, and in gelatin no liquefaction was observed.

As for pathogenicity, all the strains caused death of mice, rabbits, and guinea pigs, following intravenous or intraperitoneal injection. The minimal lethal dose varied from 10^{-3} c.c. to 10^{-6} c.c. of culture for the different strains. Four of the strains were inoculated intravenously in monkeys (*M. rhesus*) in quantities up to 0.5 c.c. of young broth cultures with no visible effect. Further attempts were made to infect rabbits and monkeys by daily spraying directly into the throat, or by nasal, drop by drop, instillation of broth cultures. The inoculations were continued for a week without inducing infection. While it is impossible to calculate the quantity of culture sprayed into the throats of the animals, it is interesting that 0.5 c.c. was instilled each day intranasally in rabbits and 1.0 c.c. in monkeys. The latter dosages were undoubtedly excessive as compared with the quantities injected intravenously or intraperitoneally, so that the conclusion is reasonable that the respiratory route probably plays little part in the natural evolution of the disease. On the other hand, when the cultures were given to white mice by drinking, the animals died of generalized infection, with the organism recoverable from the heart's blood at post-mortem. It would seem, therefore, that infection by the gastrointestinal tract is a possible means of dissemination, as suggested by Murray, Webb, and Swann,[1] and later, Burn.[12]

A serological study, also, has been made of the 22 strains. Antisera were prepared by the immunization of rabbits with both heat-killed and formalinized bacteria, the respective antisera showing no essential differences. Tests for agglutination were subsequently conducted and, as already sug-

* The strains utilized in this study were obtained from Drs. C. G. Burn, H. W. Cromwell, Philip Edwards, Robert Graham, W. M. Hale, N. P. Hudson, F. S. Markham, C. V. Seastone, E. W. Schultz, and H. W. Wadsworth.

gested in a preliminary note on the results with eight strains,[3] the different cultures separated themselves into two distinct immunological types. The pertinent data are summarized in table 1. It will be seen that of 15 strains derived from animals, 4 fell into one type, and 11 into the other. With two exceptions (a strain from a fox, and one from a calf), the different cultures appear to reflect in their type-specificity their ultimate origin, as rodent on the one hand, and ruminant on the other. It is not intended to imply, however, that the " rodent " type comes only from rodent animals, and the " ruminant " type only from ruminant animals; experimental observations in this labora-

TABLE I

Distribution of Types of *Listerella monocytogenes*

Source of Strains		Number of Strains		
		Studied	in Type I ("rodent")	in Type II ("ruminant")
Rodent animals	Rabbit	2	2	—
	Gerbille	1	1	—
Ruminant animals	Cow	8	1	7
	Sheep	2	—	2
	Goat	1	—	1
Carnivorous animal	Fox	1	—	1
Man	Meningitis	6	3	3
	Mononucleosis	1	1	—
Totals		22	8	14

tory indicate too clearly that rodent animals (rabbits, mice, and guinea pigs) may be fatally infected with strains from ruminant animals. It may be possible, nevertheless, that the original source of a given strain may be determined by the agglutination reaction. However, until further study is made, it cannot be stated whether the suggested relationship of type and animal source is only apparent or actually genuine. It is interesting in this connection that Paterson [2] suggests the possibility of three serological groupings on the basis of flagellar antigens.

The seven strains isolated from man were divided; four into the " rodent " type and three into the " ruminant " type. If the hypothesis formulated above for the serological types be confirmed by future work, it would then serve to indicate the animal derivation of strains found in human infection.

There remains to add that the two types were verified by agglutinin adsorption and specific precipitation of polysaccharides prepared from the corresponding organisms.

Since identification of *Listerella* may be confusing, a test suggested earlier is recommended for purposes of diagnosis. This consists of in-

oculating the eye of certain animals, preferably the rabbit. If the growth is moderately heavy, inoculation may be performed by simple instillation of the conjunctival sac with a drop or two of a broth culture; if, on the other hand, the growth is scanty, inoculation is more successfully accomplished by massaging gently the everted upper conjunctiva with a swab previously immersed in the culture. The inoculation is followed within 24 to 72 hours by an intense conjunctivitis with chemosis, marked exudate, and within a day or two more, invasion of the cornea, represented by infiltration and marked vascularization or pannus. This reaction has been described in detail elsewhere,[4] so that the details need not be repeated at this time. What is important now is that all 22 strains tested induced the reaction, while a large number of other bacteria, including 10 strains of *Erysipelothrix*, a somewhat similar organism, did not. The ocular reaction, therefore, appears to be not only regularly produced by, but apparently specific of the *Listerella* group.

Listerellosis in Animals

While it has been found possible to infect a number of different animals in the laboratory, it seems more logical to confine this brief discussion of listerellosis in animals to the disease as a spontaneous occurrence. For convenience, therefore, the infections will be considered as those occurring in rodent, ruminant and carnivorous animals, and in fowls. The summarized data will be found in table 2.

Table II

Principal Manifestations of *Listerella* Infections

Host		Clinical Condition
Rodent animals	Rabbit Guinea-pig Gerbille	Generalized infection; mononucleosis; glandular and hepatic involvement. "
Ruminant animals	Sheep Cow Goat	Meningo-encephalitis; occasional abortion. " " " " " " " " "
Carnivorous animal	Fox	Resembles distemper of dogs.
Fowl		Myocarditis with necrosis.
Man		Meningo-encephalitis; infectious mononucleosis (?).

(*a*) *Rodent Animals.* As already pointed out,[1] *Listerella* infection was first observed in rabbits and guinea pigs. The disease was characterized by leukocytosis, with a rise in mononuclear elements, and suppression of neutrophiles. At death, the predominant changes were focal necrosis of the liver, enlargement of the mesenteric glands, and edema of the subcutaneous tissues.

In 1927, Pirie[5] found a similar infection occurring in South Africa in the gerbille (a small, burrowing animal somewhat similar to the rat). Because the essential lesion was necrosis of the liver, Pirie named the organism isolated *Listerella hepatolytica*, although as later work showed, the organism

is indistinguishable from *Bacterium monocytogenes* of Murray, Webb, and Swann.[1]

(*b*) *Ruminant Animals.* Listerellosis in ruminant animals was first reported upon by Gill [7] when he observed the infection in sheep. Clinically, the manifestation suggests a meningo-encephalitis: first, incoördination, and then a tendency to move in large circles, thus contributing to the infection the more common name of circling disease, until the animal drops from sheer fatigue. The spinal fluid is cloudy with an increased cell count, and at post mortem there is seen congestion and meningitis, sections later revealing perivascular cuffing, and less commonly, foci of neutrophiles. The disease has since been studied by other workers,[8] and recently a detailed report has been made by Graham, Hester, and Levine [9] of outbreaks in Illinois. An interesting deviation of the infection in sheep was reported by Paterson when he observed the occurrence of 16 abortions in a group of ewes, apparently caused by *Listerella.*[10]

Jones and Little [11] published the first communication on *Listerella* infection in the bovine species. Since confirmed by Graham and his co-workers,[8] a recent report [9] gives more detailed information concerning several outbreaks of the bovine disease in Illinois. In this species, the infection manifests itself by a staggering gait, paralysis of the mandible, elevation of the head, and finally coma leading to death. The lesion is essentially meningo-encephalitic and cultures of the organism are recoverable from the medulla. The same authors described abortion as another expression of the bovine disease.[9]

While no report has been made of *Listerella* infection in the goat, Seastone [2] has supplied this laboratory with a strain derived from this animal. Paterson,[10] however, quotes Seastone by personal communication that the goat reacts to the disease as does the sheep.

(*c*) *Carnivorous Animals.* Recently, *Listerella* organisms have been isolated from an outbreak among silver foxes.[6] Apparently the disease must have resembled very much distemper of dogs, since that was the diagnosis made by the veterinarian in charge. The mortality was high, but unfortunately no histological reports are given.

(*d*) *Fowls.* Listerellosis of fowls was first observed by TenBroeck, the authority for this statement being Seastone,[2] who employed for study some of the former's strains. Since then Seastone,[2] Paterson,[10] and Watkins [10] have published accounts of the infection. In poultry, the chief sign of the disease consists of a massive myocarditis with necrosis, occasionally including the liver. It is the opinion of certain observers [10] that in the fowl, *Listerella* infection is secondary to a primary condition, such as paralysis, leukemia, internal parasitism or concurrent infection.

Thus it is seen that *Listerella* is capable of infecting various species, manifesting in the different animals an almost characteristic selectivity for the different tissues. The mode of transmission from animals of the same or different species still remains to be determined.

Listerellosis in Man

That *Listerella* infection might occur in man was demonstrated unequivocally for the first time by Burn.[12] There is reason to believe, however, that a similar condition and the same organism were actually encountered previously by Atkinson,[13] Tesdal,[14] and almost simultaneously by Schultz, Terry, Brice, and Gebhart.[15] It is interesting that in these three instances, as well as in that reported by Gibson,[16] the organism was classified as a diphtheroid. In Atkinson's and Tesdal's cases, it is assumed that the organism involved was actually *Listerella* from the descriptions submitted, but Schultz and his co-workers subsequently changed their diagnosis to *Listerella*,[2] while Gibson's strain was later reclassified correctly by Webb and Barber.[17] Since the original descriptions by the foregoing authors, other examples of the meningitic syndrome have been given by several workers.[18] It is also possible that the case reported by Cislaghi [19] is another illustration, even though no organisms were cultivated from the spinal fluid.

From the literature cited above, it may be said that as a meningo-encephalitic disease in man, *Listerella* infection has been observed in all ages from infancy to maturity, although the majority of cases thus far reported have occurred in young individuals. The principal manifestation consists of a suppurative meningitis, the spinal fluid containing an increased number of cells, particularly of the mononuclear elements. The organisms are seen in smear preparations often ingested by the mononuclear cells. Frequently there is sepsis, which may in turn lead to metastatic pneumonia and focal necrosis of the liver. Unfortunately, blood counts have not been reported in most cases, but where they have been done the indications are that there is leukocytosis with mononucleosis. Histologically, there is inflammation of the meninges, perivascular cuffing, infiltration by polymorphonuclear and mononuclear cells, and hemorrhage; the lungs may show focal pneumonia, bronchiolitis, and atelectasis; the liver discloses areas of focal necrosis, and the spleen undergoes congestion and even hemorrhage.

While a few of the cases reported have recovered in time, the disease has a high fatality. As seen in table 3, 19 cases have thus far been recorded, and of these, 12, or 63 per cent, died. It should be pointed out that the case reported by Cislaghi may not have been actually *Listerella* infection, while that of Porter and Hale was treated with sulfanilamide, which may exert a therapeutic effect on *Listerella monocytogenes*, as, in fact, their experimental studies suggest.[19] If, therefore, correction for these two patients is permissible, the fatality is correspondingly increased to 12 deaths in a total of 17 cases, or a mortality of 70 per cent.

Relation of *Listerella* to Infectious Mononucleosis

That infectious mononucleosis may be the result of *Listerella* infection was first suggested by Nyfeldt [20] when he isolated *Bacterium monocytogenes hominis* from the blood culture of a patient with the disease. In a later

TABLE III

Fatality of *Listerella* Meningitis in Man

Observer	Date	Location	Number of Patients	
			Reported	Died
Atkinson	1917	Australia	5	4
Tesdal	1934	Sweden	1	1
Schultz et al.	1934	California	1	0
Burn	1934	Connecticut	4	4
Allen *	1936	Connecticut	1	1
Gibson	1936	Scotland	1	0
Carey	1936	Massachusetts	1	0
Poston et al.	1937	No. Carolina	1	1
Wright and MacGregor	1938	Scotland	1	1
Cislaghi †	1938	Italy	1	0
Porter and Hale ‡	1939	Iowa	1	0
Porzecanski and de Baygorria	1939	Uruguay	1	0
Totals			19	12

* This case cited by Burn.[2]
† Not verified by bacteriological study.
‡ Treated with sulfanilamide, possibly responsible for recovery.

communication,[21] he reported three more successful isolations of the organism. With Schmidt,[22] he restudied the disease by cultures of the spinal fluid, again recovering the bacterium in question.

As reported elsewhere,[23] *Listerella monocytogenes* was identified in this laboratory after recovery by Dr. C. A. Pons from the blood of a patient with apparently typical infectious mononucleosis. This observation stimulated the study to be reported at this point on the possible significance of *Listerella* in this disease. The study was pursued by (*a*) blood cultures from patients; (*b*) agglutination tests with the patients' sera, using the two types of *Listerella monocytogenes* as antigens; (*c*) experimental infection in different animals; and (*d*) stimulation of "heterophile" antibody by *Listerella* under varied conditions. The diagnosis of infectious mononucleosis in the patients utilized in this study was verified by the clinical signs and symptoms, changes in blood constituents, and "heterophile" antibody—characteristic in each case.

(*a*) *Blood Cultures.* The blood from 12 patients with infectious mononucleosis was cultured, in some instances three and four times during the course of illness. The blood was seeded in quantities of 2 to 4 c.c. in veal infusion broth alone and with 1 per cent dextrose; also, pour plates were made with 1 c.c. and 2 c.c. of blood in veal infusion agar. The media were incubated at 37° C. for 10 days, when they were studied by staining and plating on blood agar before they were discarded as sterile. Except for the first culture,[23] all the others failed to give any growth.

(*b*) *Agglutination Tests.* All tests were performed with 18- to 24-hour broth cultures of both types of *Listerella monocytogenes.* In some instances,

several bleedings were made, but when only one test was done the serum used was obtained after the acute phase, usually between the first and second week of the disease. The tests were incubated for 2 hours in a water-bath set at 37° C.; then they were placed in the ice-chest until the following morning when final readings were made. In this way, agglutination tests were conducted with sera from 28 patients. Agglutination was observed in 13 instances, 3 times with the " ruminant " strain and 10 times with the " rodent " strain. The titre was never particularly high, and varied from 1:20 to 1:160. Similar agglutination tests performed with the sera of 50 " normal " individuals or patients with other diseases yielded agglutination on 3 occasions, in titres ranging from 1:5 to 1:20; in each case, only the " rodent " strain was agglutinated.*

(*c*) *Experimental Infection.* As stated earlier in this report, *Listerella monocytogenes* is virulent for rabbits, mice, and guinea pigs. Preliminary experiments indicate that monkeys are more or less resistant to the organism, although intracerebral injection may cause rapid death. Murray, Webb, and Swann [1] have already demonstrated that in both spontaneous and experimental infection there is a distinct effect on the blood picture. Thus, without affecting particularly the red blood cells or hemoglobin value, there is a distinct leukocytosis with a rise in the mononuclear elements and marked depression of neutrophilic cells. In addition, there is involvement of the mesenteric lymph glands and focal necrosis of the liver, which may or may not be the counterpart of the jaundice encountered in infectious mononucleosis. In fact, these authors conducted their studies with such thoroughness that it was not anticipated that more could be added to their results and observations. It was more for the personal experience and knowledge that experimental infection was induced in the susceptible animals mentioned above.

The experiments undertaken in this laboratory serve to confirm the studies of Murray, Webb, and Swann. The impression gained here is that while infected animals manifest the blood changes indicated, the picture suggests rather than duplicates that seen in the human. Two typical examples † of the blood changes are given in tables 4 and 5, the former representing a non-fatal and the latter a fatal infection. Both instances serve to illustrate the lymphocytic-monocytic increase induced by *Listerella*. There is, however, a certain quality to the lymphocytes in infectious mononucleosis that has not been reproduced in the animals studied. The so-called Rieder cell—lymphoblastic cell with lobulated, horse-shoe-like nucleus, and pale blue staining cytoplasm containing frequent mitochondria—while common in the

* Since going to press blood cultures have been studied in five additional patients. These have all failed to yield any growth. Agglutination reactions as described above have been conducted on seven more patients, in each instance the serum causing no agglutination. The statistics at this time reveal, therefore, one positive blood culture in 17 patients studied, and 13 of 35 patients with agglutinins present in low titres. The evidence that *Listerella* may be related etiologically to infectious mononucleosis is, therefore, correspondingly diminished.

† The writer is grateful to Miss Olga Bierbaum of the Department of Medicine of this University for these examinations.

human disease, has not been encountered in the experimental infection. Whether this difference is to be considered as an actual deviation from the characteristic change in infectious mononucleosis or a gradation dependent upon differences in the animal species is not clear from the data at hand.

The glandular involvement seen in man is reproduced to a measure.

TABLE IV

Blood Changes in Non-Fatal Experimental *Listerella* Infection
Rabbit No. 352

Day of Infection	1	2	3	4	5	6	7	8	9
Total W. B. C.	7,450	12,650	7,550	11,600	15,000	12,000	7,800	12,200	9,650
Neutrophile	41	66	42	40	50	62	40	55	67
Basophile	4	1	3	—	—	8	7	13	3
Eosinophile	—	1	—	—	6	—	—	1	—
Myelocyte	—	—	—	1	—	—	—	—	—
Lymphocyte, mature	47	22	24	21	24	16	31	17	21
" young	—	2	1	3	2	1	—	3	2
Monocyte, mature	8	8	25	22	17	11	23	11	7
" stimulated	—	—	4	4	1	2	—	—	—
Clasmatocyte	—	—	1	2	—	—	—	—	—
Total R. B. C. (millions)	4.680	4,250	3.880	—	—	3.620	3.120	3.410	3.950
Hemoglobin (%)	70	57	48	—	—	46	34	31	42

TABLE V

Blood Changes in Fatal Experimental *Listerella* Infection
Rabbit No. 354

Day of Infection	1	2	3	4	5	6
Total W. B. C.	12,050	8,400	5,800	19,950	9,800	10,000
Neutrophile	49	70	46	35	40	45
Basophile	3	4	3	7	4	1
Eosinophile	4	—	1	1	2	—
Lymphocyte, mature	35	20	23	15	16	8
" young	3	1	2	2	6	—
Monocyte, mature	6	5	16	22	27	37
" stimulated	—	—	8	15	3	14
Clasmatocyte	—	—	1	3	2	—
Total R. B. C. (millions)	5.310	4.600	4.680	—	—	—
Hemoglobin (%)	82	68	64	—	—	—

Participation by the glands in experimental infection is irregular, and the mesenteric rather than the cervical or axillary glands are affected. The splenic enlargement frequently seen in patients was not a characteristic accompaniment of the experimental infection. Histologically it is difficult to compare the tissue changes because of the inadequacy of the reports on the human tissues. Their removal has varied to such an extent as far as the

time element is concerned that the different descriptions show several discrepancies. A conservative estimate would be that although the changes stimulated by *Listerella monocytogenes* in rabbits, mice, and guinea pigs resemble infectious mononucleosis in certain respects, the experimental infection is not a strict duplication of the spontaneous disease.

(*d*) *"Heterophile" Antibody.* Antisera prepared by the immunization of rabbits with formalinized or heat-killed suspensions of seven different strains (three rodent and four ruminant) were tested by the Paul-Bunnell method [24] for agglutinins active on sheep red cells. In no instance were the sera found to contain "heterophile" antibody, despite their high titre for *Listerella monocytogenes.* Since these tests were first done in this laboratory, similar results have been published by Pisu [25] and Kolmer.[26]

Reflection on this observation suggested that possibly inactivation of the bacterial cell may have inhibited the formation of "heterophile" antibody. It may be, for example, that this antibody represents a response to some substance liberated from the tissue cell during active infection, or it may even be the result of some combination of tissue and bacterial cell. In order to acquire information on this possibility, eight rabbits were infected successfully, four with the "rodent" type and four with the "ruminant" type. Similarly, four monkeys (*M. rhesus*) were also inoculated. Trial bleedings were made up to 10 days, unless the animal died before that time, as happened in three instances. The inactivated sera were later tested for "heterophile" antibody, but agglutination of sheep red cells did not occur. It seems, therefore, that under the conditions stated, *Listerella monocytogenes* of either type is unable to stimulate the formation of "heterophile" antibody.

In attempting to derive an answer conversely, agglutination tests were undertaken with both types of *Listerella monocytogenes.* The sera used for the tests were rabbit antisera prepared by immunization with sheep red blood cells, and with genuine heterophile antigen. While both antisera contained high titres for the blood cells, they were unable to agglutinate either strain of *Listerella.*

Discussion

That *Listerella* is the cause of specific infections in various animals and fowls is obviously well-established by studies of the spontaneous disease and its experimental reproduction by several workers. The fact that such infections are widely and frequently distributed in animals suggests that listerellosis is essentially an animal affliction. What concerns the physician directly, however, is the possible spread of the condition to man. There can no longer be any doubt that while the pathways are still obscure, a purulent meningitis caused by *Listerella monocytogenes* is becoming increasingly recognized in man, and that the manifestation, while not so fatal as pneumococcal or staphylococcal meningitis for example, causes a high rate of mortality. There is a possibility, moreover, that the disease may become more commonly recognized than it is at present.

In appraising the data acquired in this laboratory on the relation of *Listerella monocytogenes* to infectious mononucleosis, the evidence is not so clear as in meningo-encephalitis. If an analysis be attempted of the individual approaches studied, each appears both to support and to discredit a direct relationship between the two factors. Thus, if the blood cultures be considered, a single recovery of the organism from repeated trials in 12 patients may imply an accidental isolation; yet, on the other hand, it must be obvious that with the disease as mild as it is, invasion of the blood stream by an organism would be an exceptional rather than a uniform occurrence.

In considering the results of the agglutination tests, the supportive evidence is that the sera of roughly half the patients tested caused agglutination of *Listerella monocytogenes*. Since the infection is mild and frequently of short duration, it is possible that insufficient stimulation is supplied by the organism to evoke circulating antibodies. While the low titres may be an expression of the same deficiency, it is also possible that they represent not a specific agglutination, but may be more in the category, for example, of the agglutination of *Brucella* organisms by the sera of patients suffering from tularemia.

As already described, the infection induced experimentally by injection of *Listerella monocytogenes* in rabbits, mice, and guinea pigs does not reproduce exactly the infectious mononucleosis of man. The dissimilarities between the two conditions may imply an actual difference in clinical entity or, instead, a difference in host reactivity to the same agent.

The most serious objection to a genuine relationship between *Listerella monocytogenes* and infectious mononucleosis resides in the inability of the organism to stimulate the formation of "heterophile" antibody, either by prolonged immunization or by active infection in animals responding with high agglutinin titres for the bacterium. Whether the conditions under which the study was undertaken were inadequate, or whether the organism lacks this capacity remains to be determined. Certainly the rabbit, which was particularly studied for this purpose, readily develops anti-sheep cell agglutinin in response to either sheep cells themselves or to heterophile antigen. It may be of further significance that rabbit anti-sheep sera and anti-heterophile sera do not cause agglutination of either type of *Listerella monocytogenes*.

Thus, it seems that the question of *Listerella* in infectious mononucleosis must await future study for a decisive answer. The results thus far acquired warrant further experimentation in order to clarify the problem raised by the isolation of *Listerella* from the blood and the appearance of agglutinins in the sera of certain patients suffering from this disease.

Summary and Conclusions

1. Bacteriological studies on *Listerella monocytogenes* suggest the ocular reaction of conjunctivitis, corneal infiltration and pannus as a diagnostic test of value.

2. The 22 strains studied divide themselves into two distinct immunological types.

3. The infections caused by *Listerella* in rodent animals are for the most part generalized, with mononucleosis and glandular and hepatic involvement.

4. In ruminant animals, the infection is primarily a meningo-encephalitis, occasionally inducing abortion.

5. In the fox, representative of carnivorous animals, the infection appears to be respiratory, resembling distemper of dogs.

6. In the fowl, myocarditis with necrosis is the important manifestation of infection.

7. In man, listerellosis expresses itself with meningo-encephalitis, with a fatality of about 70 per cent.

8. Whether infectious mononucleosis of man is also an example of *Listerella* infection cannot be answered conclusively until further study be made.

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INDUSTRIAL MEDICINE AS A SPECIALTY AND ITS RELATION TO GENERAL PRACTICE*

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During the past 25 years the introduction of medical control methods into industry has experienced a more or less stormy course of events. Industry on one side has been rather reluctant to assume its responsibilities for the protection of its employees' health, and the medical profession in general has underestimated the potential possibilities for the development of a new field in preventive medicine, and has been more or less critical of those working with industry to promote the cause. Probably there has been a lack of understanding on the part of all concerned, which, if clarified, may lead to a more coöperative working basis between industry, the medical profession and the industrial medical group.

Any attempt to clarify a situation should be preceded with at least a brief statement of the problem at hand, and in this instance it seems that the starting point might well be a statement of the actual needs of industry. Which is the more important requisite? Is it primarily surgical, or medical? If medical, is it curative or preventive?

In viewing the problem from a surgical standpoint, one must first sketch a rather brief review of the events as they have occurred from the period when industry first began its medical protective program. This time coincides with the introduction of the compensation laws in 1911. These laws made the employer financially responsible for injuries occurring while at work, established fees for the payment of hospital and surgical care, and provided pay for the injured employee. In addition they fixed payments for disabilities and death. This stimulated industry to establish two new services—first aid and safety.

In the early days the demand for surgical treatment was indeed urgent, both for first aid to the more severe injuries and for adequate treatment for minor injuries, such as abrasions, lacerations, contusions and burns. In the treatment of these minor injuries, industry recognized a means of preventing the more serious sequelae which so often follow.

The more severe injuries, requiring extensive home or hospital treatment, were then occurring with great frequency. However, with the development and application of safety measures, there came about a gradual decline in the frequency and severity of accidents. In our own Company, for example, 30 years ago it was not unusual to have 3,000 major injuries over a one year period. During the year 1939 there occurred a total of 112 major injuries among an average of 45,000 employees, spread out among units over the entire country. In many of these units there was not a single accident which was severe enough for a man to lose any time or to result in

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any partial or permanent disability. I quote these figures in an attempt to make clear the great reduction in need for surgical attention. Obviously, although this need is important, it is not nearly as important as many might be inclined to believe.

If surgery, then, is not the major requisite, how important is medical service, defining the term medical service as "medical procedures entirely exclusive of surgical"?

Modern industry is largely chemical and it would indeed be difficult to mention any present-day process of manufacture which is not, in part at least, chemical. The tremendous increase in the use of chemical compounds has brought about greater chances for exposure to not only larger quantities of chemicals but to an almost countless number of new compounds. Taking into consideration the number of compounds in use today, our factual knowledge of their toxicological action covers only a relatively small number. It is only by unfortunate experiences that we have in the past, learned that some of these compounds produce acute and chronic illness or rapid death. Practically all of this knowledge was obtained after all too many individuals had actually become sick or in many instances had died.

Industry's problem is not the *treatment* of occupational diseases, as after all, if one will be truthful about it, most cases of occupational disease get well without any treatment, when removed from exposure. The real problem is the prevention of occupational diseases by recognition of the *very earliest signs and symptoms* which indicate that the employee is getting sufficient exposure to produce physiological changes. When he has passed beyond this stage and pathological changes have occurred, medical protective methods have not been adequate. The actual development of an occupational disease is *an admission of failure* of both medical and engineering protective measures.

The problem, then, *is not how to cure men sick* of an occupational disease, but rather how to protect them against ever becoming ill of the disease; and the administration of any adequate program to accomplish this end must be more than casual—it must be *carefully planned, actively administered* and based upon a foundation of *factual* knowledge.

Obviously, no one can intelligently set up any industrial health protection program that will function adequately, unless he has an exact understanding of the hazards as they exist and a knowledge of the clinical picture which may develop. Industrial methods of production today are often very complex, involving not only the use of numerous chemical compounds but also the handling of these compounds under variable conditions, such as high temperatures and high pressures. The general industrial trend today is to so construct processing equipment as to make the entire operation as nearly closed as possible. With a completely closed process, in which dusts, fumes and personal contacts are reduced to a minimum, there remains always the possibility of leaks and the ever-occurring breakdown which is certain to be followed by exposures which are higher than normal. This is shown by

experience. No matter how safely any manufacturing process may be when installed, the medical supervision must still be carefully maintained.

My allotted time makes it impossible for me to discuss the intricate details of the investigations which are a necessary prerequisite in any industry, to the setting up of a medical protective program. In brief, these should include a careful study of the toxicity of the compounds in use, of the actual and potential exposures, and of the character of the clinical symptoms which will indicate early absorption.

The importance of this first step cannot be overstressed. It is indeed distressing to observe the number of industrial units which are in operation today in which the doctor in charge has very little conception of the working conditions within his plant, no knowledge of the toxicity of the compounds in use, and in too many instances has never been through the factory. This type of so-called industrial medicine is usually conducted by the part-time physician who does not seem to fully appreciate his responsibilities. Such a service is unfortunately stimulating in his factory group a false sense of security. The plant manager knows little of his industrial hazards and feels that once he has taken on a physician to manage the medical program, his hazards are then well under medical control. I recently made an inspection of a plant in which there was a hazard due to exposure to a volatile solvent. The plant physician, a very reputable man in his community, had been doing the medical work for several years. He had never gone through and studied the plant. He examined all employees before entering the plant at the time of employment but never repeated his examination after that. He stated very positively that there had been no cases of occupational poisoning in his plant.

Everyone who has studied the solvent employed in the above instance knows that it is toxic, producing both acute and chronic symptoms with severe mental changes. The exposure in this particular plant is sufficiently high to produce numerous cases of chronic illness which can be easily recognized by simple examination methods.

Medical supervision of this type is to be severely criticized. It all too frequently leads to unfortunate misunderstandings with the employee's family physician. The family physician may not be too familiar with his patient's plant exposure, but does know that there is undoubtedly an association between the man's work and his illness. The plant physician on the other hand claims the illness did not occur at the plant.

With an intelligent understanding of existing hazards plus some knowledge of the physical and mental requirements of all jobs in the plant, applicants can be intelligently selected who will fill these jobs with the least possibility of physical damage to themselves. This selection must be made at the time of the employment examination and in this part of the work lies great opportunity for one to develop his diagnostic ability.

In the past, much just criticism has been directed against physical examination of applicants for employment, because these examinations were

made simply for the purpose of excluding individuals who showed even the most minor physical defects. *Such a program is unfair and if continued will create an insurmountable problem of unemployment.* Anyone who has had experience in doing this work knows that it is impossible to find enough physically perfect men to fill any plant of appreciable size, and physical defects are not often a bar to selected employment.

The employment examination must, if it is to be sufficiently accurate to enable one to properly place applicants, include a chest roentgen-ray, complete urinalysis, a serological test for syphilis, a blood count, and a reasonably accurate estimation of visual acuity for both near and far vision. The Snellen test is by no means satisfactory. Our experience with the telebinocular has been most helpful and from the industrial standpoint it offers the best method available at the present time.

It is not my purpose to go into the details of how to make a physical examination but rather to point out that one is of necessity almost forced to use most of the available clinical methods because of the difference between examining a sick patient and an applicant for employment. Applicants for employment are in general not inclined to give a truthful medical history concerning either their present or past complaints. Their purpose is to convince the examiner that they are physically fit for the job, rather than come to him for treatment of their ills. So they will deny many pertinent facts. This unfortunate condition was largely brought about by the early physical examinations and the indiscriminate rejections. One of our problems now, is to educate the applicant to the realization, that for his own protection and future health there are certain types of work to which he is not suited. For example, applicants with arrested pulmonary tuberculosis should never be employed in positions where they will be exposed to gases and dusts which are known to be pulmonary irritants. Individuals with any circulatory disturbance must be excluded from exposure to certain chemical compounds which we know act directly upon the circulation, and so on, taking into consideration every organ of the body and the possible chances of aggravating any existing disease.

We sometimes find it necessary to reject an applicant for the position for which he has been selected. He then will consult with his family physician who tells him that there is no reason why he should not have been accepted. Undoubtedly his family physician is sincere in making this statement, but unfortunately he has not the proper conception of the risk involved and fails to realize that what was done, was so done for the protection of the future health of his patient. The physician outside of industry finds it hard to understand why we cannot accept cases, which we know are risks, for a trial period in order to observe what happens. Here it must be pointed out that any unfavorable developments in any case of chronic or arrested disease are compensable, as the aggravation of an existing condition. Therefore it becomes readily understandable that in addition to the risk to the employee, there is the added risk of compensation expenses to the employer.

These risks are often very high as shown by our experience in aggravated tuberculosis, for example, in which our costs average $12,000.00 a case.

Under conditions such as have just been mentioned there exists an opportunity for better understanding between the industrial physician and the general practitioner if each will contact the other and discuss the hazards involved in their respective factories and communities. The problems of the chemical industry are too many and too varied for those who are not directly connected with industry to entirely understand. The internist is not expected to render either service or advice, without consultation, to those patients whose ailments fall within the field of the specialist who has studied and been trained in roentgenology, or neurology, or surgery or other specialties.

In any well organized industrial medical service, every employee who is examined, whether it be for employment or periodic checks, is advised to consult with his family physician for the treatment of physical defects or illness found at that time which are not of occupational origin. Industry, in general, is not interested in treating those cases for which they are not responsible and as a matter of fact is only interested in guiding these cases into the proper medical hands in order that they may improve their general health and thereby become more efficient and safer workers. The number of cases referred to the general profession by the industrial physician is truly great. For example, we examined 4200 individuals in our central office during 1939 and over 2000 of these people were advised to consult with their physicians for the correction of existing physical defects or illness. To one who is not experienced in examining a group of so-called well people, these figures might tend to indicate an abnormally high percentage of defects. However, it is indeed amazing when one examines any group of people to find how few, regardless of occupation, do not have some defects that require either surgical, medical or dental attention.

A few figures from the above group will give some ideas as to the incidence of a circulatory disease: 258 had a systolic pressure of 150 or over; 75 had a systolic pressure of 99 or under; and taking 90 as the upper limit of normal diastolic pressure, we found 420 who had 90 or above, some as high as 140; 112 had organic heart disease with audible murmurs. A total, in this group, of 865 showed evidence of circulatory disease.

Thus, in addition to the duties involved in the administration of an adequate medical program for the prevention of occupational diseases, we have the added problem of persuading large numbers of people to improve and protect themselves, insofar as medical aid will accomplish this objective, against acute and chronic diseases while in the early stages before they have become disabled. My purpose in mentioning these cases is to point out to those of the medical profession who persist in maintaining that the industrial physician is robbing them of work which rightfully belongs to them, that they are really having referred to them many cases which would otherwise not be seen until much farther advanced.

We have another group consisting of 1250 syphilitics, all of whom are gainfully employed; every one is under the care of his or her family physician for adequate treatment. Each one must frequently present satisfactory evidence to show that he or she is getting adequate treatment regularly.

Knowledge of the action of the compounds handled, the symptoms to be expected and the careful selection of applicants who can work under these known conditions safely must always be followed up by periodic physical examination. In this examination lies the most important part of the work, as almost the entire program of prevention is dependent upon these repeated examinations provided they are done with the proper frequency and are of such a nature as to reveal early signs of absorption.

The frequency of the periodic examinations depends upon the rapidity with which the compounds in question may be absorbed and produce symptoms. The type of examination must be such as to reveal the earliest symptoms of absorption, not the symptoms of acute illness. This phase of industrial medicine may truthfully be said to require one with special knowledge and training to organize and execute the program.

In addition to understanding the mode of action and the clinical picture that indicates early absorption, it is important to realize that any examination program must be as practical and as simple as possible. When dealing with a sick patient in the hospital the physician orders blood counts, blood chemistries, roentgen-rays and many other procedures as often as necessary, and the patient submits with more or less complacency. If, however, one attempts to handle a group of workers and asks them to submit to more or less painful procedures too frequently, they will sooner or later rebel. Furthermore, in industry one must always remember that any medical examination must be made on company time and time away from work means loss of money to the employer and increased costs of production. Medical costs are eventually charged against production and an increased cost of even so small an amount as one-tenth of a cent a unit may mean added costs of thousands of dollars over a period of one year. I mention costs because it is quite obvious that medical men, in general, fail to realize the importance of the economic problem. There is in general the feeling that industry should pay regardless of the costs because they need the service. Industry does need the service and will pay willingly if and when it can be convinced of the need for the service, that the service will be the answer to the problem at hand, and will lead to savings in compensation costs and potential medico-legal suits.

The results of the periodic examination determine whether the employee shall continue with his work or whether he should be removed from exposure and placed, temporarily at least, in other work. If he shows signs of early absorption, then the industrial physician must determine whether the faulty exposure is due to general working conditions or careless methods on the part of the worker himself. The latter is often the cause and obviously it is of no avail to recommend an entire change of working condi-

tions, which will never suffice under such circumstances. It is sometimes necessary to dismiss workers who are consistently careless and thereby constantly subjecting themselves to unsafe exposures.

The follow-up of medical conditions in the plant requires frequent and often prolonged visits to the actual operations where conditions may be studied firsthand. Air analyses are sometimes valuable but should never be used as a criterion of safety. From the medical standpoint, we are interested in knowing whether the men are being affected rather than what the concentrations in the air might be. Air analyses are of value to the engineering department who use them as a guide to determine whether their ventilating devices are functioning according to expectations. It is unsafe to set any concentration of a compound in the air as a safe one unless medical examinations are to be used as an index of health among the men.

In the time allotted to me I have tried to outline briefly some of the major principles of industrial medicine and at least indicate the importance of inaugurating a program based upon an intelligent understanding of the conditions that should be met. Any such program, if it is to be adequately followed, must necessarily require sufficient time on the part of the physician who undertakes it, if he is going to give his best efforts toward the prevention of occupational diseases and the promotion of better health.

If the work is done properly, the examinations made accurately, and the follow-up conscientiously pursued, the opportunity for real, worthwhile, scientific medicine is available. On the other hand, the work can be nonproductive of preventive results and scientific interest, and a sheer waste of time, if performed as too much of it is being performed at the present time.

In conclusion the following recommendations are made:

1. Know the toxicity of the compounds and their mode of action.
2. Understand the potential hazards and job requirements on the plant.
3. Select employees who can safely fill the jobs.
4. Watch every one of them by proper periodic examinations.
5. Refer all illnesses and ailments other than occupational to the family physician.

PANCREATITIS: AN ANALYSIS OF TYPES AND CAUSES*

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THE picture brought to mind by the term acute pancreatitis is that of a necrotic, hemorrhagic gland, in the extreme state gangrenous, which has produced an upper abdominal catastrophe with severe pain and tenderness, collapse and death.

In fact the very names used to designate acute disease of the pancreas carry the significance of extreme disease, thus *acute hemorrhagic* pancreatitis or, more recently in usage, *acute hemorrhagic necrosis,* whereas in actual anatomical study neither hemorrhage nor necrosis of conspicuous degree need be found. Consequently, the older name, *acute pancreatitis* may still be considered a better one to designate the class, reserving qualifying terms for use when they are appropriate.

Since Opie [1] reported the production of acute hemorrhagic pancreatitis by a gall stone lodged at the ampulla of Vater in such a way as to convert the biliary and pancreatic ducts into a common channel for the flow of bile into the pancreas, the usual conception has been that the mechanics of the disease must be of such a nature and that bile is the offending or exciting factor.

It seems timely that attention be drawn to the frequent occurrence of grades of the disease not constituting a major clinical or anatomical catastrophe and, further, to the fact that other causes of pancreatitis than entry of bile or even duct obstruction may be of importance.

Rich and Duff [2] in a comprehensive study of pancreatitis not only drew attention to epithelial metaplasia in the ducts as a possible cause of obstruction but really gave the clue which has led to our conception of the composite manner in which the severe grades of the disease may be developed from several different beginnings.

Their demonstration that liberated trypsin is sufficiently irritating to cause destruction of tissues and in contact with blood vessel walls leads to necrosis and rupture with consequent hemorrhage lays the ground for a conception that from whatever cause secretion may be liberated the tendency is toward a hemorrhagic type of inflammation, but that unless action of trypsin is sufficient to erode blood vessel walls hemorrhage may not be a considerable feature.

Thus one might expect that from the occurrence of several different orders of conditions, while the primary event is not alike, the ultimate development may well be the same and we might expect to see the extreme case of acute hemorrhagic pancreatitis or even the state of gangrene super-

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vene from such different beginnings as from duct obstruction, with or without the entry of bile, from vascular closure, or from infection, either primarily of the ducts or outside them.

Pancreatitis from Vascular Occlusion

Interest in application of this idea arose from a case of typical acute hemorrhagic pancreatitis not based upon duct obstruction but upon embolism of the pancreatic artery.

This occurrence was in the case of a white man of 52 years who, after drinking whiskey, suffered an acute abdominal crisis with severe pain and tenderness and collapse. He gave a history of two similar attacks of pain the last several months previously. At necropsy there was massive hemorrhagic necrosis of the tail of the pancreas, without discoverable evidence of duct disease or obstruction, but with infarction from a thrombus-embolus in the supplying artery. The origin of the embolus was a mural thrombus situated upon atheromatous patches of the aorta above the pancreatic artery.

The occurrence of acute pancreatic disease from vascular closure is usually minimized by students of pancreatitis, but with this case as a base for interest, an investigation of necropsy material in our service for the past ten years disclosed two other cases of this origin among a total of eighteen. The suspicion is aroused that occurrences of this order may be more common than we ordinarily believe and that at least some of the instances of acute disease of the pancreas in which no evidence of duct obstruction are found may be really of vascular origin.

One incident in the story of the first case may merit a further word: the fatal attack occurred after drinking whiskey. This association has been noted not infrequently in previous studies of the disease. Weiner and Tennant [3] give alcohol as a probable factor in 66 per cent of 38 cases of acute pancreatitis. Rich and Duff suspect that alcohol may stimulate trypsin production in pancreatic secretion and thus accentuate its action. The drinking of whiskey in the case cited here could hardly have had a bearing upon the embolism; but it may have accentuated the action of released tryptic secretion.

Both of our other instances of arterial occlusion occurred in patients whose primary disease was malignant hypertensive vascular disease. One was a negro man of 36 who in addition to hypertension had old rheumatic heart disease and was further suffering an attack of lobar pneumonia and an unexplained gaseous edema of the arm which had followed the injection of fluid at this site. The other was a negro man of 30 years whose vascular disease was complicated by bronchopneumonia and acute gastroenteritis. In neither was clinical evidence of pancreatic disease observed in life and what part it played in the fatal issue is problematical. In both there was extensive arteriolar sclerosis and arteriolar necrosis in the pancreas, much like that seen in the kidneys in both cases, and there was extensive organizing thrombosis of arteries and veins.

Rich and Duff have called attention to the similarity of the arteriolar necrosis of malignant hypertension to that produced by the action of trypsin; also to the occurrence of thrombosis in acute pancreatitis.

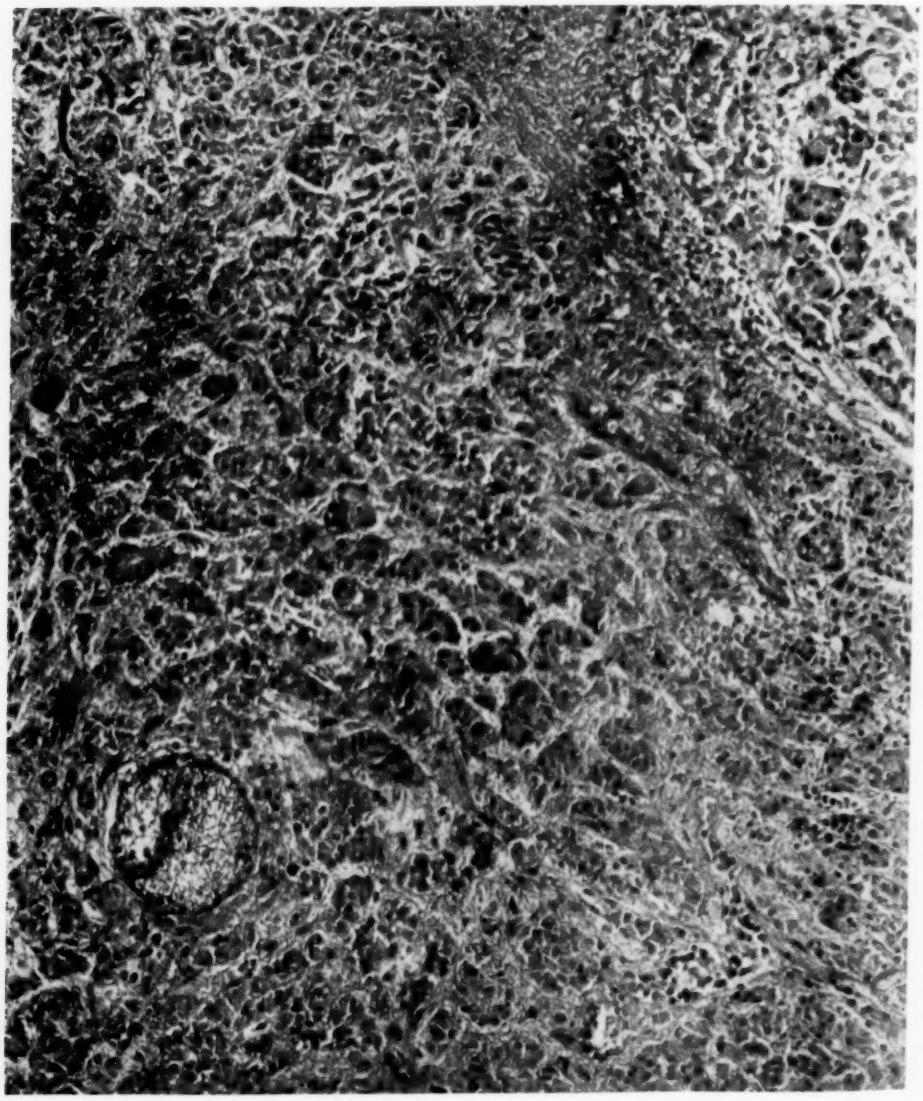

FIG. 1. Acute necrosis of pancreas from vascular occlusion. × 210.

In none of these cases was there evidence of duct disease or obstruction, no obstructing condition, no dilatation or accumulation of secretion. Instead there was a massive type of necrosis, with surrounding hemorrhage and active inflammatory infiltration and fat necrosis (figure 1).

Diffuse and Focal Pancreatitis

In seven of the other fifteen cases the basis for acute disease seemed unrelated to either duct or blood vessel obstruction. In four of them the inflammatory state was interlobular, consisting of diffuse edema and polymorphonuclear leukocytic infiltration of the interstitial tissues (figure 2).

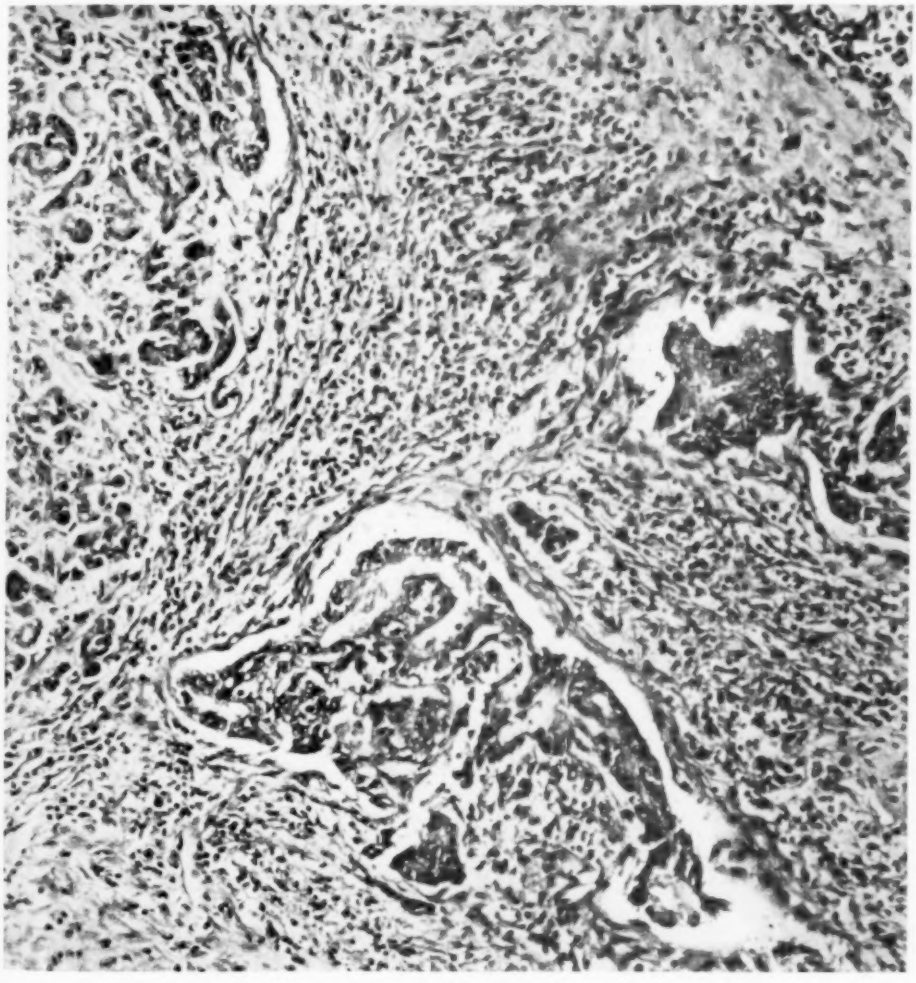

Fig. 2. Acute diffuse pancreatitis, cause undisclosed. × 210.

There was no necrosis and no hemorrhage. It seems that the term acute interstitial pancreatitis would be appropriate in these cases. None of them gave clinical evidence of the pancreatic condition found at necropsy, and its importance is of uncertain status.

One of these was a negro man of 21 who died of acute endocarditis, acute nephritis and cerebral infarction. Another was an aged negro man

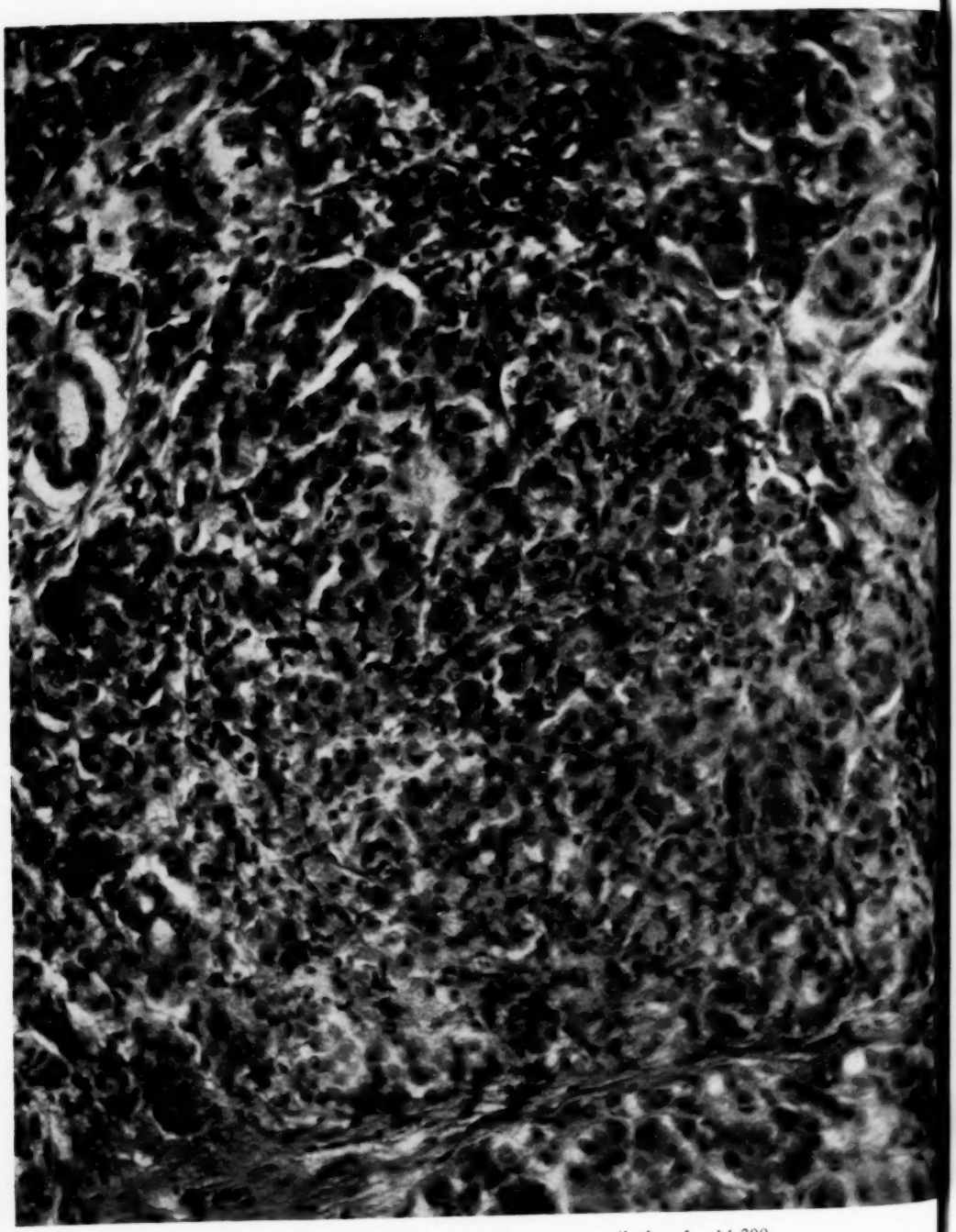

FIG. 3. Focal acute pancreatitis, cause undisclosed. × 300.

with an infected carcinoma of the pancreas. A third was a negro man with a gunshot wound of the abdomen. The last of the four was a negro woman of 33 with lobar pneumonia, acute pleurisy, acute pericarditis, and tricuspid valvulitis.

The basis for the pancreatitis in two of these four cases seems obviously to have been local infection with extension through the pancreas. The origin of the apparent infection in the other two is not known, but they were both infectious cases. It seems likely that this particular type of pancreatitis is on an infectious basis, and in the extreme grade could well conform to the old class of suppurative pancreatitis. Should ducts become sufficiently involved in such a process there is no reason why the typical picture of acute hemorrhagic pancreatitis should not supervene.

Three of the seven revealed a different picture, that of intralobular rather than interlobular distribution, with small foci of acinar necrosis and leukocytosic infiltration (figure 3). The first was a negro man of 40 with malignant hypertensive vascular disease, atheroma with mural thrombi of the aorta, and abscess of the scrotum. It was a question whether to relate the state of the pancreas to vascular disease, embolism or infection. The second was a negro girl of 12, the only child in the group, and the only case showing duct epithelial metaplasia (not conspicuous). While the pancreatic disease seemed minor in extent and degree there appeared no other explanation for her death. The third was a negro man of 50 with generalized arteriosclerosis, bilateral carcinoma of the kidneys and acute pleurisy.

In none of these three cases were clinical symptoms of pancreatitis observed.

The pathogenesis of this type showing acute focal pancreatitis, is not clear. There was no evidence of duct obstruction in any except possibly the girl. Three modes of development suggest themselves: small vessel occlusion, ductule obstruction, focal infection.

Obstructive Pancreatitis

As would be expected the largest group of the series is undoubtedly based upon duct obstruction. It included eight of the eighteen cases, although in only four was the obstructing condition discovered. In none of the eight was there evidence of such a state as to lead to flow of bile into the pancreas from the bile duct.

The identifying feature of this class of pancreatic disease is obstruction of some part of the duct system evidenced by dilatated ducts containing accumulated secretions, whether or not the obstructing object or condition is found. Accumulated secretion may appear in the ducts as smooth hyaline substance or as blobs of coagula mixed with stringy substance (figure 4). Rich and Duff thought that this apparently inspissated secretion might itself be a primary cause of obstruction in some cases, but since it is to be found where some other definite obstructing condition is present and since

there is no apparent reason for inspissation to occur otherwise it is probably better looked upon as effect and not as cause.

The walls of ducts may be observed to be necrotic, ruptured and leaking secretion. The spreading of the secretion is attended by necrosis of framework and fat, whether or not extension into the glandular tissue occurs. When this does take place the influence is characteristically from the periphery of the lobule inward, rather than central as in the focal group, or rather than *massive* as in the vascular occlusion group.

FIG. 4. Obstructed pancreatic duct. × 210.

Hemorrhage is logically a characteristic feature, thanks to the explanation of Rich and Duff, whether it be extensive enough to give the gross findings or not. Even with minor hemorrhage, the smudgy degeneration of blood vessel wall is apt to be seen.

Leukocytic collections are seen about escaped secretion and necrotic tissue, varying in proportions probably with the duration of the state.

The first patient of this group was a white woman, 71 years of age, with carcinoma of the head of the pancreas, there being no recorded findings to tell of the terminal pancreatic state. The next was a negro woman of 45, with an unruptured abdominal aortic aneurysm. The aneurysm was diagnosed, and pain in the pancreatic region was attributed to it. The third was a negro man of 70, with a pancreatic duct stone. This man was a sufferer from general and renal arteriosclerotic disease, the apparent cause

of his death, and pain in the right lower chest area was thought to be cardiac. The fourth case was a negro man of 37 who died of chronic nephritis and uremia. The obstructing condition was a papilloma within one of the duct branches. There were no clinical symptoms significant of pancreatic disease. In fact, the lesion was minor in extent, but, curiously, involved hemorrhage into the islets.

Of the four cases showing the features of obstruction, but without discovery of the obstructive condition, the first was a negro girl of 20 with chronic nephritis and abscesses of the liver and spleen. She had suffered severe abdominal pain for two weeks, the abdomen was tender throughout and there was a suggestion of rigidity. She was stuporous and her blood urea was 30 mg. per cent and her creatinine 10 mg. per cent. The next case was a negro man, 57 years of age, with generalized arteriosclerosis and cerebral hemorrhage. There were no symptoms significant of pancreatic disease elicited. The third was a white woman aged 34, a victim of chronic alcoholism. The fatal attack occurred after drinking whiskey. She was irrational and then comatose and exhibited convulsions. There was slight general abdominal rigidity and she would flinch on deep abdominal pressure, but was not aroused. The systolic blood pressure was 170 mm. of mercury and the diastolic 126; there was marked elevation of the levels of blood urea and creatinine. The clinical diagnosis made was uremia. The fourth case was that of a negro man of 60 years with general, renal and coronary arteriosclerosis. Tenderness was elicited over the abdomen and he had pain in the lower right and left sides. He died of progressive heart failure and bronchopneumonia. The pancreas showed typical duct system obstruction but little or no hemorrhage.

Epithelial Metaplasia

The possible importance of duct epithelial metaplasia as an obstructive cause cannot be lightly passed by, even though in a series like this, where particular search was not made throughout the gland, it was seen only once. In those cases where no obstruction is found grossly at necropsy careful section should be made of the gland with this in view.

Weiner and Tennant found metaplasia in three blocks from 63 glands in acute disease, in five blocks from 84 normal glands, and in twenty-four from 114 in fibrous disease, and this apparently from the examination of just one section from each block.

The most conspicuous example I have encountered was in a gland from a woman who died of arteriosclerotic disease with coronary occlusion. She was told that she had diabetes nine years previously, but had apparently recovered. There was no glycosuria or hyperglycemia during her last illness. The pancreas in this case exhibited marked old scarring, with practical obliteration of acini in some lobules, although islets and ducts were present in these same lobules (figure 5). The islets generally were very large, some being apparently normal in cellular structure but many extensively hy-

alinized. Probably at the time when she had diabetes there had been a more or less acute catastrophe to acini and islet tissue, leaving many of the latter permanently disabled, for which compensation had occurred in hypertrophy of undamaged islet tissue and probably regeneration of islets also.

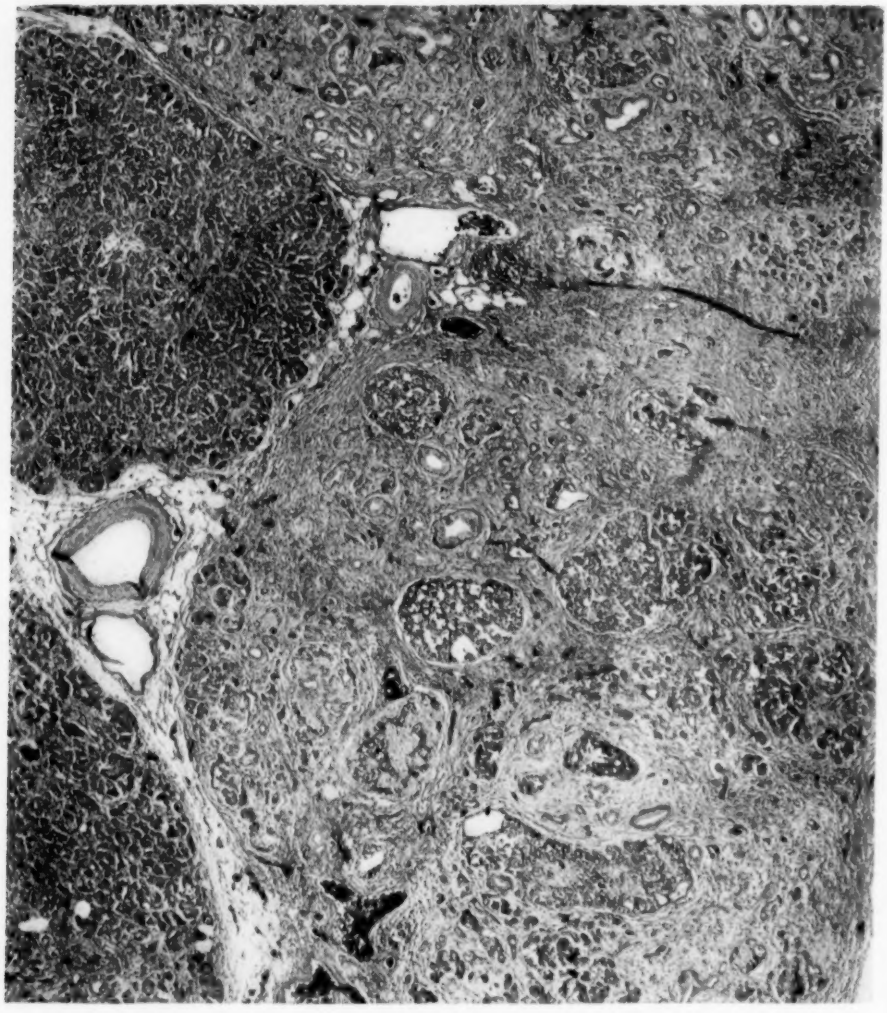

FIG. 5. Old scarring of pancreas with hyalinization of some islets and hypertrophy of others. Case of diabetes nine years ago, now recovered. × 52.

Duct epithelial metaplasia was very extensive and exhibited the state in various grades of advancement. In the incipiency there occurs between the lining columnar cells and the basement membrane nests of polygonal or rounded cells of uniform size, and with uniform nuclei containing a fine chromatin network and a tiny nucleolus. The outline of these cells is not distinct (figure 6). They accumulate into a nodule pushing the lining

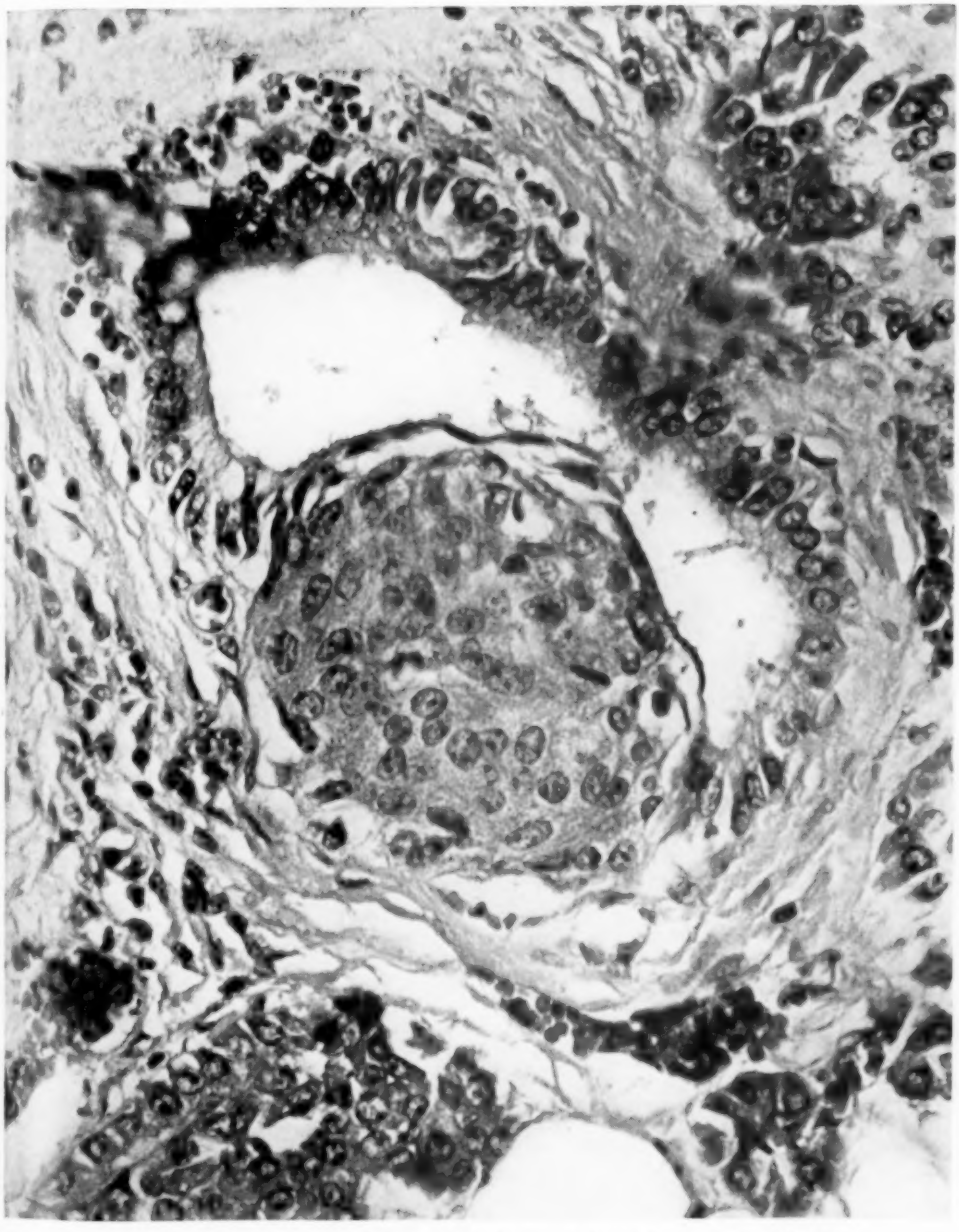

FIG. 6. Nodule of epithelial metaplasia in small duct of pancreas. × 810.

epithelium inward and causing it to become flattened and finally quite atrophic, it however remaining distinct from the metaplastic focus. In the advanced stage the whole duct lining may be so displaced, although the

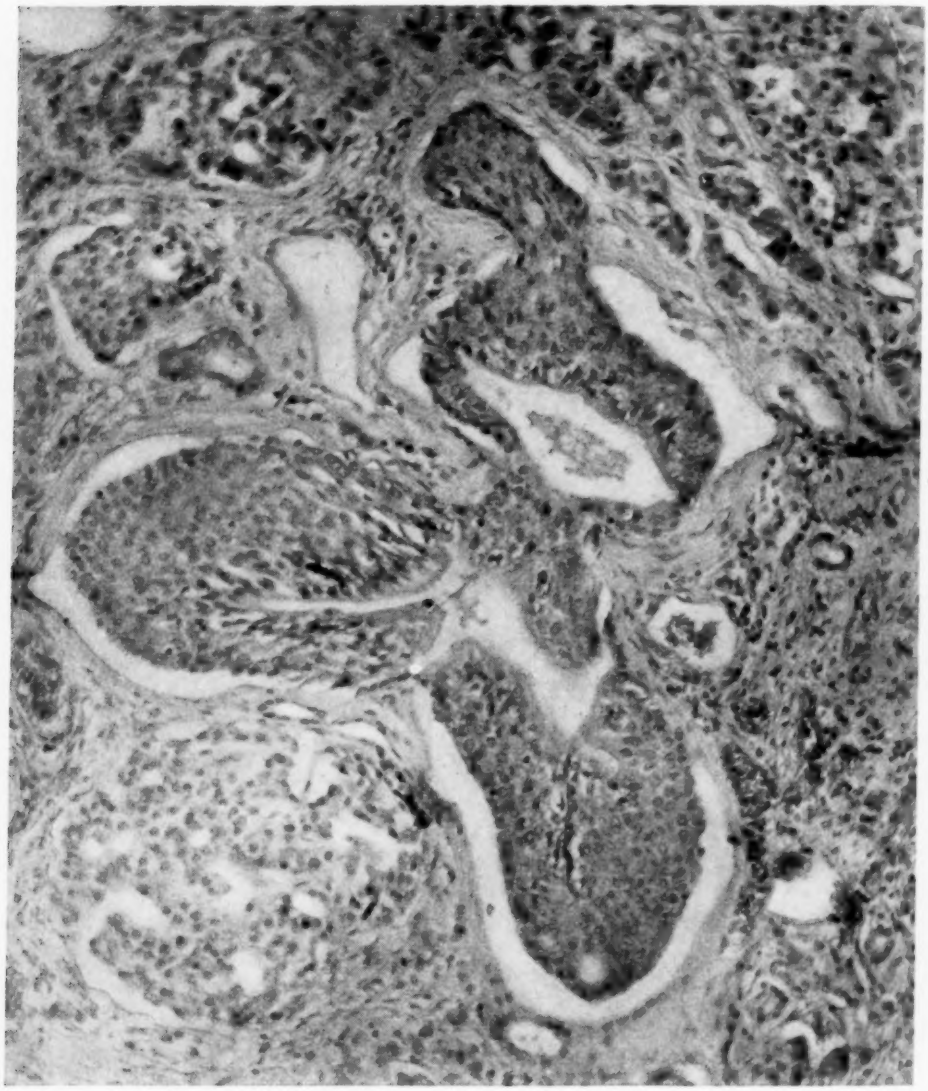

FIG. 7. Complete epithelial metaplasia in duct of pancreas. × 240.

original epithelium may be still seen in fragments upon the surface (figure 7). This tends to reduce the calibre of the affected duct.

Just how much actual obstruction is thus produced is problematical. In the gland here cited there is little or no evidence of dilatation or of accumulation of secretion, and while it is impossible to say that the scarring

FIG. 8. Formation of islet within wall of pancreatic duct. Case of diabetes nine years previously, now recovered. × 515.

of the gland, even of islets was not the product of acute pancreatitis on such an obstructive basis, it does seem that persistence of the metaplasia should have produced persistent effect of the same order, which appears not to be the case.

It is very interesting in this same gland to note the resemblance of the cells in the metaplastic foci to those of the islets. They are very similar, although at times the former are more compact. Of further interest is the occurrence of nodules of unquestionable islet cells in the same basal location as the metaplasia, that is definitely within the duct wall, between the basement membrane and the columnar cell lining and pushing the latter inward and causing its flattening and atrophy (figure 8).

The real nature of this metaplasia is not known. May it be related to an attempt to form islet cells? A further question is, may it not be a part of chronic disease, as other similar epithelial metaplasia may be?

Summary

Of this series of 18 cases of acute pancreatitis only two apparently gave such clinical evidences of the disease as should have led to a diagnosis of the state. None was actually diagnosed.

In the majority probably recovery would have occurred so far as the pancreatic disease was concerned. This would likely have led to a state of scarring in some degree, a so-called chronic pancreatitis. If this may be true, then is it not likely that similar sub-clinical grades of acute disease of the organ occur as complications of pathological states from which recovery does occur and is this not a logical explanation of the scarring of the pancreas commonly encountered?

While duct obstruction does apparently furnish the main etiological event in pancreatitis it does not appear necessary that it lead to entry of bile nor that bile is at all an essential factor. It appears that vascular occlusion and probably infection cause no inconsiderable proportion of acute disease of the gland. While the lesions produced by these factors are often minor, non-necrotic and non-hemorrhagic, yet these lesions may be sufficient in some instances to cause rupture of ducts and release of secretion into contact with blood vessels. In this event the end result will tend to be identical, irrespective of the pathogenesis. There will be produced that pathological picture which we know as acute hemorrhagic pancreatitis or acute hemorrhagic necrosis of the pancreas.

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MEDICAL APPLICATION OF ULTRAVIOLET RADIANT ENERGY *

By FRANK H. KRUSEN, M.D., F.A.C.P., *Rochester, Minnesota*

THE use of ultraviolet radiation in the treatment of disease has been most extensive, but much of the literature on the subject has been poorly written and is of an unconvincing nature. It is, therefore, essential that one make a careful analysis of the writings on this subject and accept only that which seems to have proved its claims by properly controlled studies.

INDICATIONS FOR ULTRAVIOLET IRRADIATION

Diseases of the Alimentary Tract. There is now sufficient evidence to indicate that ultraviolet irradiation may be of distinct value in the treatment of tuberculous peritonitis and enteritis. Since this condition is one of the most frequent complications of pulmonary tuberculosis, occurring as it does in from 50 to 80 per cent of all fatal cases, any measure that will be of benefit is of the utmost importance. Ultraviolet irradiation is one of the most important factors in the arrest and treatment of intestinal tuberculosis.[1] In a survey of 8087 routine postmortem examinations, evidence of pulmonary tuberculosis was found in 886 cases and of intestinal tuberculosis in 233 cases. The ratio of pulmonary to intestinal tuberculosis was, therefore, approximately 4 to 1.[2] Of 180 patients with intestinal tuberculosis treated at Saranac Lake, 65 per cent of those treated with ultraviolet light were alive, whereas of those not treated only 17 per cent were alive at the time of the report. At the Trudeau Sanatorium, of a series of 106 patients with intestinal tuberculosis, 88 per cent of those treated by ultraviolet light survived, whereas only 25 per cent of those not so treated survived.

Following the use of the mercury quartz lamp in the treatment of intestinal tuberculosis, tubercle bacilli often disappear from the stools; pain, nausea and vomiting are relieved, but the diarrhea and intestinal disturbances tend to resist the longest.[3]

In the treatment of tuberculous peritonitis the best results are obtained in the ascitic type. In abdominal tuberculous adenitis it may be unwise to temporize with light therapy, since it has been reported [4] that in more than three-fourths of the cases it is possible to excise the affected glands.

Ultraviolet irradiation has been recommended in the treatment of pylorospasm.[5] It is possible that when this condition, as seems often the case, is associated with calcium deficiency, ultraviolet irradiation may be of value.

Diseases of the Circulatory System. In the treatment of secondary anemia it has been suggested that one of the important factors in an ideal

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program consists of adequate exposure to ultraviolet radiation.[6] There is considerable similarity between anemia and rickets (a disease cured and prevented by ultraviolet irradiation when there is an adequate intake of calcium and phosphorus).[7] In both diseases there is lowered gastrointestinal acidity (pH) which interferes with the absorption of calcium and with the absorption of iron, with a resultant decrease in the amount of iron available for blood regeneration.[8] In both diseases changes in the bone marrow and modifications in the types of cells may be seen. Ultraviolet irradiation may be beneficial in the treatment of either disease.

In a study conducted for a period of more than eight years in an artificial light clinic for school children [9] it was found that, in anemic children, after 12 or more exposures to irradiation from a carbon arc lamp the amount of hemoglobin increased by approximately 10 per cent. Another controlled study of the use of ultraviolet irradiation in 54 cases of secondary anemia [10] showed greater increases in hemoglobin and in the number of erythrocytes and leukocytes in the treated than in the control group. It has been suggested [11] that further studies of patients with secondary anemia may indicate a possible influence of ultraviolet irradiation on the chemical constituents of the blood. Although various studies indicate that ultraviolet radiation may be a useful adjunct in the treatment of secondary anemia, there are still insufficient data to indicate the exact value of this therapeutic measure.

In hypertension, various observers [12, 13, 14, 15, 16] have shown that ultraviolet irradiation does produce transient reductions in blood pressure. The work of Laurens and his co-workers in this field has been most convincing. As a therapeutic measure, however, it is doubtful whether ultraviolet irradiation can be considered more than a slight adjunct to the treatment of hypertension.

In carbon monoxide poisoning, ultraviolet irradiation has been employed because of the fact that Haldane and Hartridge showed that the dissociation of carbon monoxide and hemoglobin was markedly increased under the influence of ultraviolet light. Such treatment has been found to be beneficial.[17, 18]

Diseases of the Respiratory System. Many articles have been prepared, pro and con, with regard to the use of general ultraviolet irradiation in the prevention and treatment of the common cold. At Cornell University [19] small groups of male students were irradiated with minimal erythema doses of ultraviolet rays once weekly during the winter months. It was reported that there was an apparent reduction of the incidence of colds ranging from 27.9 to 55.5 per cent. At Vanderbilt University [20] an investigation revealed that, in the management of common colds, there was a decided improvement in cases in which ultraviolet irradiation was used.

At the Cook County Hospital [21] ultraviolet irradiation was recommended in the treatment of chronic coughs. It was said to have a stimulating effect on general metabolism and on resistance to infection provided the optimal dose was not exceeded and the patient was free from fever.

On the other hand, some investigators have been of a contrary opinion; thus it has been concluded [22] that although the mercury quartz lamp has been used extensively to enhance individual resistance to colds, well-controlled studies on both infants and adults have nevertheless failed to corroborate claims for its value. Hill and Clark [23] thought that there was little to support the view that ultraviolet irradiation was capable of increasing a person's natural resistance. Still other investigators [24] have performed experiments similar to those conducted at Cornell, with results which were for the most part negative, although they did find that in certain tests the resistance of the irradiated group was greater than that of the control group. Still other investigators [25] observed 363 adults for 35 weeks; during the first 31 weeks approximately half the group were given frequent ultraviolet irradiations, a single minimal erythema dose being applied either to the chest or back at each treatment. The incidence of colds during the period of study was slightly higher in the irradiated group than in the control group; however, it should be pointed out that failure to benefit the treated group may have been due to inadequate dosage. Only a quarter of the body was treated at any session and the dose was not increased at subsequent sessions. It is generally agreed that to produce beneficial systemic effects a series of irradiations of the entire body should be given and that the dose should be gradually increased.

Further investigations will be necessary before final conclusions can be drawn concerning the value of ultraviolet irradiation in treating common colds.

In the treatment of pulmonary tuberculosis there has likewise been much controversy concerning the use of ultraviolet irradiation. Although ultraviolet light is frequently used in Europe for the treatment of pulmonary tuberculosis, in this country it has often been thought to be dangerous. It has been especially stressed that there is danger of producing pulmonary hemorrhage. My own controlled studies [26] on 60 patients who were receiving routine sanatorium care indicated that hemoptysis did not contraindicate the judicious employment of heliotherapy, and a number of other investigators [27, 28, 29] have reached similar conclusions following controlled studies. It has been said that treatment which brings about improvement in the general health of the patient is the best means of combating pulmonary, as well as surgical, tuberculosis.[3]

Observations [30] on 115 patients treated by carbon arc irradiation led to the conclusion that patients with minimal, moderately advanced, and even far advanced pulmonary tuberculosis may be benefited by graduated exposures provided the patient's temperature does not rise above 37.5° C. (99.5° F.) and his general physical condition is satisfactory.

In Denmark light treatment of pulmonary tuberculosis is now almost universal, and in Britain detailed results in a series of 123 cases led to the conclusion that, provided patients are carefully selected, chronic pulmonary tuberculosis may be treated not only with safety but with good results.[31]

Recently a number of writers in the United States [32, 33, 34, 35, 36] have expressed a similar opinion. It has been reported [37] that clinical experience will convince one of the value of the mercury-quartz-vapor lamp in the treatment of pulmonary tuberculosis in children. Tuberculous infants who show excessive pulmonary infiltration even with cavity formation may recover.

Although I believe that, judiciously employed in conjunction with routine institutional care, light therapy may be of value as an adjunct in the treatment of pulmonary tuberculosis, its indiscriminate use is fraught with danger. Of 71 competent observers, 47 obtained favorable and 24 either poor or no results following the use of ultraviolet irradiation in the treatment of pulmonary tuberculosis.[38] This indicates an almost 2 to 1 preponderance in favor of the judicious application of ultraviolet radiation. Far advanced toxic or advancing active, exudative pulmonary tuberculosis should not be treated by light therapy, but incipient pulmonary tuberculosis (especially in children) and nontoxic lesions which have reached the stage of chronicity may be benefited by the careful administration of small doses of general ultraviolet radiation. Abundant rest, an increased intake of food, and proper hygienic measures are more important in the treatment of tuberculosis than is light therapy, which is merely an adjunct to these other measures.

Diseases of the Bones and Joints. In a study [39] of 22 children with bone and joint tuberculosis who were treated throughout the winter and spring with radiations from a high-intensity carbon arc light, it was found that the majority showed a rise in the blood count, a tendency to gain weight, and likewise a marked improvement in the local tuberculous lesions.

An extensive study [40] on the nonoperative treatment of tuberculous joints of the lower extremities revealed that, over a period of years, 65 per cent of the adult patients under treatment for all extrapulmonary tuberculous lesions showed a definite, though usually inactive, pulmonary tuberculosis. Conservative treatment by heliotherapy, in conjunction with routine care, was the method used in this large series of cases. Of 437 patients with tuberculosis of the bones and joints and 72 with osteomyelitis (nontuberculous) who remained on an institutional regimen for three months or longer, the following conditions were revealed on dismissal: apparently recovered, 53.8 per cent; arrested, 23.1 per cent; improved, 10.7 per cent; unimproved, 7.8 per cent; died, 4.5 per cent. A follow-up of these patients revealed that between 80 and 87 per cent were working; between 8 and 10 per cent were ambulant but unable to work; and between 3 and 5 per cent were confined to bed. It was concluded that such conservative treatment usually resulted in healing with useful motion. Operative interference should not be attempted until after prolonged heliotherapy has been tried.

Bernhard,[41] as a result of 25 years' experience, believed that in the treatment of surgical tuberculosis heliotherapy was the method of choice. In his first 1000 cases of surgical tuberculosis in which patients were treated

by heliotherapy, 858 were "cured," 120 were improved, 14 were unimproved, and eight died, a mortality rate of only 0.8 per cent. Six of the unimproved later died, raising the final mortality to 14, or 1.4 per cent.

In osteomalacia, fragilitas osseum, and delayed union of fractures, all of which may be due to faulty calcium metabolism, ultraviolet irradiation may be of value. In a study [42] of experimental fractures of the fibula in 25 normal dogs and 80 normal rats, measured amounts of carbon arc radiation were administered during the period of healing. During this period 73.9 per cent of the fibulas of animals irradiated with "sunshine carbons," 26.9 per cent of those irradiated with "C carbons," and 41.3 per cent of those of controls, healed. The average healing time for fractures was 3.7 days shorter when the animals were irradiated than when they were not. In fractures of the long bones it has been reported [43] that among patients who were given irradiated ergosterol there was an increase in the density and the amount of callus as compared with a control group of patients. These changes were greatest in children and in the aged, and they began to appear about three weeks following injury. On the other hand, in rabbits and rats given, respectively, 3 and 1.25 gm. of irradiated ergosterol by mouth, there was no increase in the rate of healing or amount of callus in fractures of the tibia and fibula.[44]

In rats on which parathyroidectomy has been performed, with consequent parathyroid deficiency, calcification does not occur regularly in the callus following fracture if calcium is also lacking in the diet; under such conditions irradiated ergosterol promotes calcification of callus.[45]

It seems logical to presume that ultraviolet irradiation has little influence on healthy individuals whose calcium metabolism is normal; but it would seem that it might be of value for patients with faulty calcium metabolism who sustained fractures.

A number of authors [46, 47, 48, 49, 50, 51, 52] have recommended the use of ultraviolet radiation both for atrophic and hypertrophic arthritis. Although there is no specific effect, it is believed by many clinicians that ultraviolet irradiation is of value, particularly when there is an associated secondary anemia or when the patient has been confined to bed for a long period.

It has been claimed that ultraviolet irradiation tends to counteract the decalcifying process in the bones and to have an accessory nutritional influence in managing the anemia, debility and allied conditions so frequently found in chronic infectious arthritis.[48] It has, however, been pointed out that chronic infectious arthritis can continue as a progressive crippling disease even in the Arizona desert unless therapeutic measures other than sunlight and climate are utilized.[53]

It has been recommended that, in cases of chronic infectious arthritis in children, reasonable exposure to sunlight or quartz lights be utilized during the winter months.[54] Ultraviolet irradiation has been especially recommended in the treatment of psoriatic arthritis.[55, 56] A combination of crude, cold tar ointment and ultraviolet irradiations is applied to the psoriatic

lesions, and heat, massage and exercise are applied locally to the involved joints.

Diseases of the Genitourinary System. It has been reported [57] that in a series of 26 cases following nephrectomy for renal tuberculosis ultraviolet irradiation proved to be a most helpful therapeutic measure for the cure of the tuberculous sinuses and visceral ulceration incident to the disease. It has likewise been said [58] that in tuberculosis of the genitourinary tract surgical treatment frequently offers prompt relief if combined with postoperative heliotherapy.

Direct irradiation of the bladder for the treatment of tuberculous ulceration or cystitis has been recommended by a number of observers.[59, 60, 61]

Diseases of the Eye. Following an 18-year study,[62] ultraviolet irradiation was reported to have proved its worth in the treatment of diseases of the eye. Such treatments had, for example, reduced the proportion of losses in ulcus serpens from 30 to 6 per cent; ultraviolet irradiations had likewise produced favorable results in other diseases of the cornea, conjunctiva and sclera. Excellent results have been reported in the treatment of corneal ulcers by accurately localized ultraviolet irradiation.[63, 64]

Ultraviolet radiation is likewise often of benefit in the treatment of tuberculous lesions of the eye.[65] A study [66] of the combined use of local and general ultraviolet irradiation for the treatment of tuberculous lesions of the eye in 100 children revealed some improvement in every case.

Diseases of the Ear. It has been claimed [67] that irradiation by means of a Kromayer lamp with a small quartz rod will in many instances abort furunculosis of the external auditory canal. Combined local and general ultraviolet irradiations have been reported [68] to be of definite value in the treatment of tuberculosis of the middle ear.

There is little evidence that ultraviolet radiation is of value in the treatment of chronic otorrhea, for which it has occasionally been recommended; it has been pointed out [65] that even a thin layer of mucus or pus will filter out the ultraviolet rays and prevent any favorable action.

Diseases of the Nose. Ultraviolet irradiation has been recommended as an adjunct to the surgical removal of tuberculous lesions of the nose.[69] It has likewise been said [70] that ultraviolet irradiation is of value in the treatment of infected wounds and certain nasal dermatoses, and its use has been suggested [64] for ulcerations of the nose, especially septal ulcers. Ultraviolet rays have likewise been said to be of value in the treatment of lupus of the nasal mucosa.[71]

Diseases of the Throat. Combined general and local ultraviolet irradiation has been recommended in the treatment of tuberculous laryngitis.[72, 73, 74] Strandberg reported a series of 203 cases of tuberculous laryngitis in which the patients were treated by general ultraviolet irradiation followed by cauterization.[75] One hundred and thirteen patients were reported as cured of the disease of the larynx and the majority of the others were said to have improved. Thomson [76] challenged these results and said that 32 patients

with pulmonary tuberculosis had been treated according to the Finsen plan without any striking evidence of benefit. In only two or three of these cases might some improvement have been claimed.

Nevertheless, Stevenson [75] observed 320 cases of tuberculous laryngitis in which 38 of the patients showed clinical cure, 101 were improved, 81 were unimproved, 59 were worse, and 41 died. All of Stevenson's patients received routine sanatorium care, vocal rest and various local applications to the throat as well as ultraviolet irradiation. It is, therefore, impossible to say which was the most important factor in treatment.

In a study [77] of 452 cases of pulmonary tuberculosis, tuberculous laryngitis was present in 19.2 per cent of the cases. It was felt that reflected sunlight was occasionally of value in supervised cases, particularly during the early stages. It would seem that in tuberculous laryngitis general and local ultraviolet irradiation, in conjunction with routine care, may be of some value in selected cases and is certainly worthy of trial. Several observers [78, 79, 80] have felt that the local applications of ultraviolet light were a valuable adjunct.

Miscellaneous Diseases. In rickets it is believed [81, 82, 83] that ultraviolet irradiation furthers the absorption from the intestine of either phosphorus or calcium, or both. It is probable that the hydrogen-ion concentration is the limiting factor in such action. It has been shown by a number of investigators that, to produce beneficial effects in the treatment of rickets, it is necessary to administer only comparatively small doses of effective ultraviolet radiation. For example, a single weekly exposure to one erythema dose of ultraviolet rays was sufficient to produce healing of rachitic lesions in infants.[84] Irradiations with a mercury quartz lamp, front and back, for four to five minutes once weekly until approximately 100 minutes of exposure had been given, was sufficient to effect cure in a series of 43 rachitic nurslings.[85]

Irradiation, even with heavy doses of ultraviolet light, did not prevent rickets in rats which had been placed on a ricket-producing diet provided they were prevented from licking their fur or eating their excretions. If, however, the rats were shaved, the skin sterol was then activated by irradiation, absorbed, and exerted antirachitic effects.

It has been shown [86] that the pro-vitamins D exhibit pronounced ultraviolet absorption. Of the 8 to 10 pro-vitamins D which are said to exist, only two, ergosterol and 7-dehydro-cholesterol, appear to be very common. When irradiated, these pro-vitamins become extremely active, since 5 mg. of either are equivalent in potency to one liter of good cod liver oil. Direct irradiation of the skin by ultraviolet rays may be specific in the treatment of rickets.

Results comparable to those obtained in the treatment of rickets may also be obtained by the use of ultraviolet irradiation in cases of tetany and spasmophilia.

Among the unusual applications of ultraviolet irradiation may be men-

tioned its use for diagnostic purposes,[87, 88, 89, 90, 91, 92] for the identification marking of newborn infants, for the purpose of producing hardening of the nipples prenatally,[93] and for the sterilization of air in operating rooms.[94, 95, 96] It has been pointed out that prenatal irradiation and the irradiation of the nursing mother are efficacious in the prevention of rickets in the child,[97] and that direct irradiation of cows will impart an antirachitic potency to their milk.[98]

Summary

Ultraviolet irradiation has been used extensively but indiscriminately in the practice of medicine. There is, however, a rather large number of conditions * in which there is evidence that ultraviolet irradiation is, or gives promise of being, valuable. Among these conditions may be mentioned tuberculous peritonitis and enteritis, calcium deficiency diseases, secondary anemia, carbon monoxide poisoning, pulmonary tuberculosis (as an adjunct), tuberculosis of bones and joints, atrophic and hypertrophic arthritis (as an adjunct), tuberculosis of the genitourinary tract, ulcus serpens, corneal ulcer, tuberculous lesions of the eye, ear, or nose, nasal ulcerations, tuberculous laryngitis, rickets, and tetany and spasmophilia.

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* Because elsewhere in this symposium Dr. Anthony C. Cipollaro has discussed the dermatologic aspects of light therapy, the indications for the use of ultraviolet radiation in dermatology have not been discussed in this paper.

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DIRECT NONPENETRATING INJURIES OF THE HEART *

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THE increasing physical hazards and strains of civilization have served to stress the importance of trauma as a cause of disease. The medical evaluation of this factor as it pertains to cardiology is so confused that it is not unusual to find equally competent observers on opposite sides of the same question. This paper is presented as a clinical study of only one aspect of this problem, namely, direct nonpenetrating injuries of the heart.

A survey of standard [1] and specialized texts [2] leaves the impression that this clinical entity is either seldom diagnosed or else is very rare; and in the current literature only is the subject considered to any extent.

Direct nonpenetrating injuries of the heart may result from a blow, a kick or punch over the precordium, the striking of the chest against hard objects, crushing injuries of the thorax with or without fractures, steering-wheel type of accident, sudden compression of the abdomen, the jarring of the chest contents as in falls from a height and perhaps from massive doses of roentgen-rays applied locally.[3] There are usually external signs of injury such as redness, swelling, discoloration, increased local heat and, fractures of the bony parts, but usually no direct open path between the skin and the heart. In the young and occasionally in the older individual the heart may be severely damaged by this type of injury without any local signs.[4, 5, 6, 7, 8, 9, 10] Bright and Beck [7] have demonstrated that fatal cardiac damage may follow the application of a nonpenetrating force to any part of the chest or abdomen [11] and also exploded the popular fallacy that only diseased organs can be damaged by direct trauma. In all types of heart injuries it may be safely stated that the more extensive the trauma, the more extensive the damage. In the laboratory [7, 10, 12, 13, 14] and at the bedside it has been demonstrated that diseased organs tolerate less trauma than healthy structures. This fact aids in understanding why in given instances a minimum of trauma may produce a maximum of change.

CASE REPORTS

Case 1. W. P., a 13-year-old boy, was admitted to the Flower-Fifth Avenue Hospital on May 29, 1938. One hour before he had fallen from the roof of a five story building into the street below. He was in shock, semi-conscious, had multiple fractures of the right ribs, seventh and eighth dorsal vertebrae and an associated complete transverse myelitis. Twenty-four hours later he was examined by the medical service and at this time did not have any cardiac complaints.

The movements of the right chest were decreased and associated with marked tenderness and diminished breath sounds. The left lung showed exaggerated normal vesicular breathing. The heart was enlarged to the left and the apex was just out-

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side the left mid-clavicular line in the fifth interspace. The sounds were of extremely poor quality and lacked the characteristic normal snap. The rhythm resembled the so-called tick-tick type previously described by Beck.[15] The first apical sound was equal in intensity to the second and the second aortic equalled the second pulmonic. The rate was 125 per minute. The patient was conscious and to a great extent had recovered from his initial shock. Hourly blood pressure readings were as follows:

On Admission	—112/56	8th hour	— 84/46
1st hour	— 80/20	9th hour	— 98/70
2nd hour	— 64/?	10th hour	— 96/50
3rd hour	— 70/20	11th hour	— 98/56
4th hour	— 76/20	12th hour	— 98/50
5th hour	— 80/30	13th hour	— 96/44
6th hour	— 84/28	14th hour	— 96/45
7th hour	— 85/60	15th hour	— 98/48

Serial electrocardiographic studies showed the following (figure 1):

June 1: A low T_1; inverted T_3; high take-off of T_4 (1) and T_4 (2).
June 7: Increase in the voltage of R_1, T_1, T_2 and T_3; the latter showing a tendency to be upright; T_4 (1) showed a return to a normal take-off and T_4 (2) showed a low voltage and was notched.
June 13: T_1 was diphasic; T_3 was now upright; T_4 (1) showed a low voltage and was inverted; T_4 (2) showed a low voltage and was notched.
June 23: T_1 was almost iso-electric; T_4 (1) was upright and notched.
June 30: T_1 was beginning to be upright and the T_4 was low and notched.
July 19: T_1 and T_3 were flat and of low voltage.
August 2: T_4 (2) was inverted.
September 7: T_4 (1) was upright and T_4 (2) was still inverted.
November 7: Essentially the same as September 7.

The patient remained at the hospital for about five months and was examined repeatedly. The heart sounds except on one occasion were noted as faint, distant, muffled and of poor quality. The blood pressure rose to 110 mm. mercury systolic over 60 mm. diastolic and remained at that level. The final diagnosis was a fractured spine, fractured ribs, a transverse traumatic myelitis and contusion of the heart caused by a direct nonpenetrating trauma.

Comment: A contusion of the heart was suspected because of the type of injury, quality of the heart sounds, the tick-tick rhythm, the initial falling arterial blood pressure and the changing electrocardiographic picture. The precordium did not show any signs of injury nor did the patient have any cardiac complaints. It was impossible to determine how much cardiac function had been lost because of the bedridden condition of the patient. The diagnosis rested on demonstrable objective findings.

Case 2. H. M., a 17-year-old boy, was admitted to the surgical service of the Flower-Fifth Avenue Hospital on June 3, 1938. While trying to walk on a picket fence he lost his balance and fell a distance of four feet, striking his breast bone sharply against a picket point. He immediately felt nauseated, vomited, and experienced a great deal of difficulty in catching his breath. These symptoms continued and interfered seriously with the patient's ability to carry on his ordinary activities. In the past a heart murmur had been noted, but direct questioning indicated that cardiac compensation had not broken down.

The examination showed a swelling the size of a small egg over the lower end of the sternum. The roentgenogram revealed a transverse fracture of the lower segment of the gladiolus of the sternum. The heart was enlarged to the left; the sounds were muffled, distant, and lacked the characteristic normal snap. The first apical sound was equal in intensity to the second and the second pulmonic was louder than

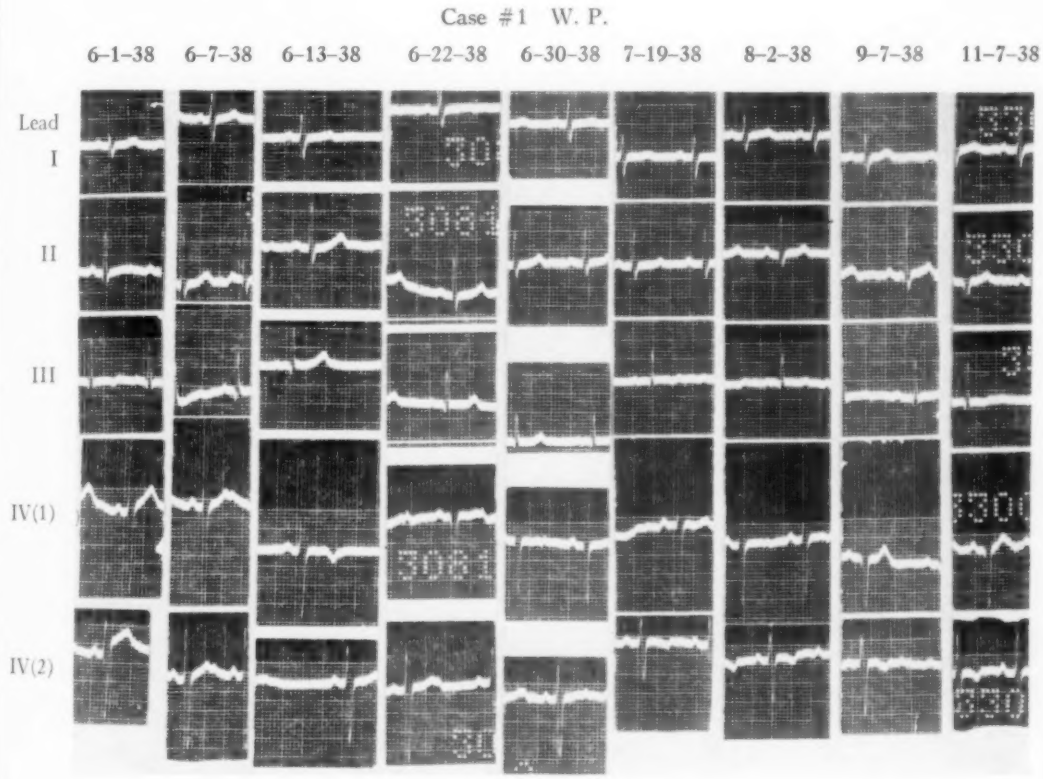

FIG. 1

the second aortic sound. A short diastolic murmur was present over the aortic region. Normal sinus rhythm was associated with a rate of 96. The blood pressure was 110 mm. mercury systolic over 0 mm. diastolic. The rest of the examination was essentially normal.

The electrocardiographic findings (figure 2) were as follows:

June 11: An inverted T_3 and a high take-off of T_4.
September 24: Inversion of T_2 and T_3, a more normal take-off of T_4.
October 28: T_2 and T_3 were upright and a higher take-off of T_4.

Four months after his injury the patient had fully recovered, with no cardiac complaints. The apex of the heart was located in the mid-clavicular line; normal sinus rhythm was present; the rate was 78; and an occasional extra systole could be heard. The sounds were of fair quality; the first apical sound was louder than the second and the second aortic was greater than the second pulmonic. The diastolic murmur which previously had been heard over the aorta was now heard over the pulmonic region. The blood pressure in both arms was 110 mm. mercury systolic over 60 mm. diastolic. A simple bending exercise was normally performed.

Comment: This boy was in good clinical cardiac health until he sustained a direct nonpenetrating injury of the chest. Immediately afterwards he developed signs and symptoms of mild cardiac insufficiency. This damage was temporary as judged from the examination at the end of four months. This injury evidently was capable of producing the aortic diastolic murmur, the high pulse pressure and the associated changing electrocardiographic picture.

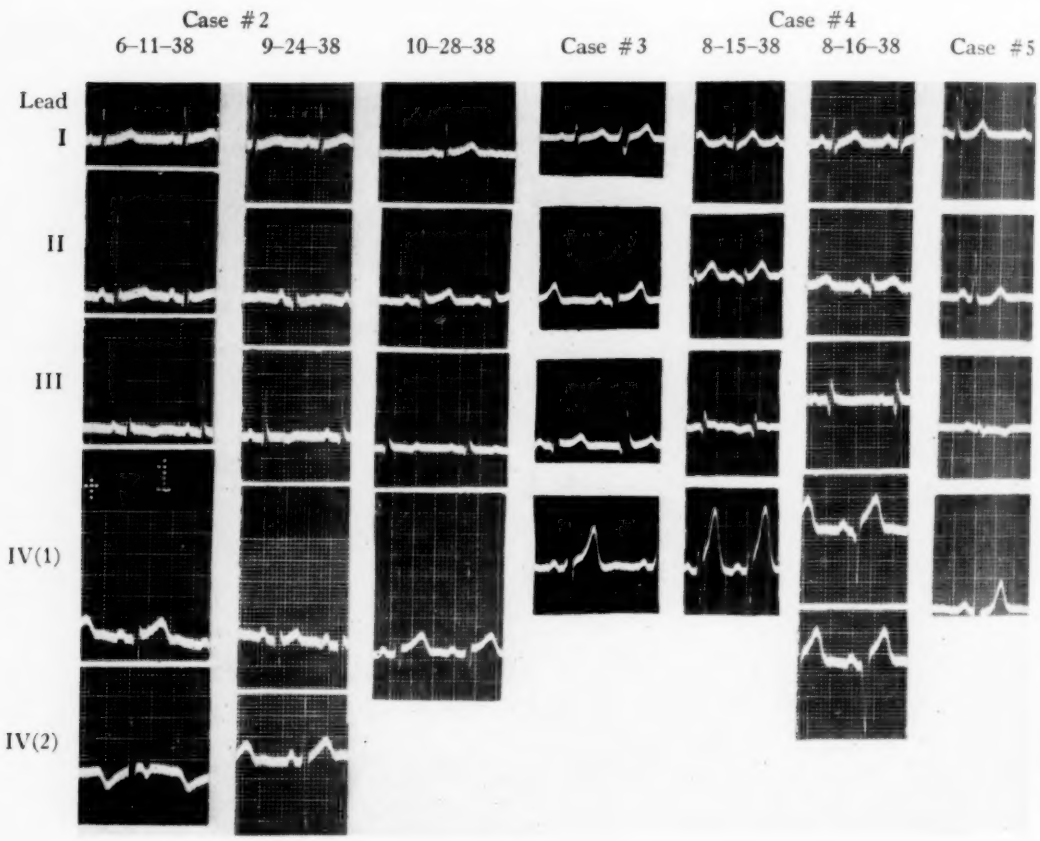

FIG. 2

Case 3. J. S., a 21-year-old white male, had always been in good cardiac health until he sustained an accident on June 28, 1938. His chest was caught and crushed between two type cases, each weighing approximately 300 pounds. After the injury he felt very weak and dizzy, and was conscious of substernal and generalized pains in his chest. No fractures were present. He was treated with bed rest and sedatives. On attempting to work, he became markedly dizzy, heart conscious, short of breath, very pale, broke into a profuse sweat and complained of substernal pressure. These symptoms persisted and were aggravated by any exertion.

The patient was young, high strung, nervous and alert. The heart was normal in size, the sounds were of good quality and showed the normal relationship to each

other. After a simple bending exercise a faint systolic murmur was heard at the apex and the pulse rose to 180, but did not return to normal within three minutes. The normal sinus rhythm was disturbed by numerous extra systoles which were not abolished by exercise or pressure over the carotid sinuses. The blood pressures were normal. Radiographic studies were normal. The electrocardiogram showed numerous extra systoles of nodal origin.

Comment: This patient was in good clinical cardiac health until he sustained a direct nonpenetrating injury of the chest. He immediately developed symptoms associated with extra systoles and a tachycardia. Though the exact pathology in this patient's heart is a matter of speculation, yet it must not be forgotten that a fair percentage of experimental animals showed extra beats after direct injuries.[12, 16, 7, 13, 14] It is possible that an irritable myocardium resulted. Though the consensus of opinion at present indicates that extra beats are usually the result of tobacco, tea, coffee, fatigue and psychogenic influences, yet to this list should be added the possibility of a traumatic origin. These extra systoles did not account for the clinical syndrome, and the final diagnosis was a cardiac neurosis in association with an effort syndrome.

Case 4. G. P., a 38-year-old male, was first seen on October 14, 1938. While surfbathing a week previously he was struck in the chest by a large wave and thrown over. On arising he felt sharp pains in the heart region which radiated to both shoulders. In spite of treatment these pains continued intermittently and on October 15 became very sharp and crushing in nature, and were associated with severe sweating and weakness. The past history was essentially normal.

The patient was well developed with a rather ruddy complexion. The heart was normal in size; the sounds were of good quality and had the normal relationship to each other. Normal sinus rhythm was present with a rate of 120. The blood pressures were normal. The fluoroscopic examination suggested a slight enlargement to the right. The electrocardiographic findings were low and slurred QRS complexes in all limb leads and a tachycardia. There was a beginning Q_2, a definite Q_3, a high take-off of T_2, T_3, T_4 and a low R_4. Electrocardiographic studies the next day at the Flower-Fifth Avenue Hospital revealed further changes (figure 2) which served to confirm the clinical impression of an acute coronary closure. The blood count was 111 per cent hemoglobin, color index 0.69, red blood cells 8,100,000, white blood cells 21,000, polynuclear leukocytes 84 per cent, lymphocytes 7 per cent, monocytes 9 per cent.

Comment: This patient was in good clinical health until he was struck in the chest by a wave. Immediately after his injury he developed signs and symptoms of a coronary thrombosis. Though his injury was not severe, extensive pathology developed. It is possible that he had an underlying blood condition which resembled polycythemia vera, though similar blood pictures may follow a coronary closure. In addition there may have been some coronary sclerosis. The trauma was the exciting factor.

Case 5. A. F., a 55-year-old male, fell from the top of a ladder on July 3, 1937 and struck his chest. He was stunned, unable to move, and complained of severe pains throughout his chest. He was removed to a city institution where he remained for 10 days with the above complaints and a laceration of the right shoulder. Roent-

genographic examination failed to show any fractures. At this institution the examination of the heart and the Wassermann test were negative. He was discharged, but continued to complain of precordial distress, increasing shortness of breath, and an inability to carry on his previous work. These symptoms were progressive and made worse by any kind of exertion. Although the patient has been repeatedly examined, no definite objective findings were present until four months after his injury. He had always been in good physical health, was married, had six children who were living and well, and denied lues by names or symptoms.

The precordium showed a pulsating area about 2 cm. in diameter located in the second interspace about 3 cm. to the right of the sternum. Over this area there was a systolic thrill and a loud harsh systolic murmur which was transmitted to the neck. There was an increase in the area of supracardiac dullness which extended to the above pulsation. The heart was small; the sounds were of good quality; and normal sinus rhythm was present. The blood pressure on the right was 110 mm. mercury systolic over 70 mm. diastolic and on the left 112 mm. mercury systolic over 68 mm. diastolic. The rest of the examination was essentially normal. The roentgenographic studies showed a normal heart shadow with a moderate diffuse enlargement of the aorta and a saccular aneurysmal dilatation of the ascending portion which in the oblique position pointed anteriorly. The electrocardiogram suggested myocardial damage. The Wassermann and Kahn tests, which had been negative, now were strongly positive. The final diagnosis was luetic aortitis with an aneurysm of the ascending portion of the aorta.

Comment: This patient was in good clinical health until he sustained a direct nonpenetrating injury of his chest. He then developed cardiac symptoms though repeated examinations did not reveal any obvious pathology until four months later, when the Wassermann test became positive and objective signs of an aneurysm appeared. It is logical to assume that the injury started a chain of events culminating in the above described picture. The exact mechanism of the trauma is a matter of conjecture though it is possible that the aorta may have been injured locally and thus produced a vulnerable spot for the syphilis to localize in.

Case 6. S. G., a 49-year-old male, had always been in good cardiac health. On October 9, 1937, he fell from a 12-foot ladder striking his head, shoulders and chest. He was admitted in an unconscious state to the Broad Street Hospital and remained there eight days complaining of dizziness, headaches, nausea, heart palpitation, precordial distress, nocturia and frequency. The above symptoms had not been present before the accident, and continued to persist after his discharge. He was married, had three children who were living and well. His wife had not had any miscarriages, though 25 years previously he had been treated for a chancre.

The eyes reacted to light and accommodation. The heart was enlarged to the left; the sounds were of good quality and normal sinus rhythm was present with a rate of 90. The first apical sound was louder than the second and the second aortic was greater than the second pulmonic. The superficial chest and arm veins were enlarged and pulsated. This phenomenon had always been present. The blood pressure was 100 mm. mercury systolic over 60 mm. diastolic. A definite Romberg's sign was present. The Wassermann test was strongly positive. Radiographic studies showed a dilatation of the first portion of the aorta. The electrocardiograms were essentially normal except for a high take-off of T_4. The diagnosis was luetic aortitis and possibly myocarditis. Six months later there was a further decrease in cardiac efficiency with the development of an intracranial thrombosis.

Comment: This patient was clinically well until he sustained a nonpenetrating injury of the chest. He then developed progressive signs and symptoms of cardiac insufficiency. Syphilis was the underlying cause while trauma was the precipitating or exciting factor.

Case 7. L. K., a 55-year-old male, was in good cardiac health and had been employed as a plumber for a great many years. On December 8, 1936, he fell from the top of a six foot ladder and struck his chest sharply against the floor. This injury caused him to vomit, left him weak and produced a sensation of pressure over the breast bone and in his abdomen. These symptoms continued and were aggravated by physical exertion. A progressive shortness of breath began to develop, and approximately six weeks after his injury the patient collapsed completely. At this time, the electrocardiograms showed severe myocardial damage and a first stage heart block. After a prolonged bed rest the above symptoms still persisted.

The left pupil was larger than the right; the eye grounds showed a moderate sclerosis. The heart was normal in size and the sounds were of poor quality. Sinus rhythm was present with a rate of 65. The first apical sound was equal to the second and the second aortic was equal to the second pulmonic. The blood pressure on the right was 130 mm. mercury systolic over 85 mm. diastolic, and on the left 150 mm. mercury systolic over 85 mm. diastolic. Roentgenographic studies showed a mild dilatation of the ascending aorta with a normal heart shadow. The electrocardiographic studies showed an increased P–R interval with some slurring of the QRS.

Comment: The patient was in good clinical cardiac health until he sustained an injury. He then developed progressive signs and symptoms of a cardiac nature which finally culminated in an acute episode. There was probably a fair degree of coronary sclerosis which can be considered as the underlying factor, and the trauma precipitated clinical heart disease.

Case 8. J. B., a 66-year-old white male, had been in comparatively good cardiac health until he slipped on some icy stairs and fell, striking his upper back rather severely and sustaining a fracture of the transverse process of the fourth lumbar vertebra. In bed his only complaints were pain in the back and nervousness, but exertional shortness of breath appeared when the patient was allowed up.

Moderately advanced generalized arteriosclerosis and a coarse intention tremor were present. The heart was enlarged to the left; the sounds were of fair quality with an occasional reduplication of the first sound at the apex. The first apical sound was equal to the second and the second pulmonic was greater than the second aortic. The liver was palpable at the rib margin. The blood pressure in the right arm was 130 mm. mercury systolic over 50 mm. diastolic and in the left 180 mm. mercury systolic over 86 mm. diastolic. The Wassermann test was negative. Fluoroscopy revealed a moderately enlarged left heart and dilatation of the aorta. The electrocardiogram showed a slurring of the QRS, a low take-off of T_4, and a P–R interval which measured 0.28 sec. (digitalis).

Comment: Though elderly, this patient did not develop clinical heart disease until after his injury. No cardiac complaints were present while in bed, but cardiac symptoms did appear when he was allowed up, at which time the heart enlarged and decompensation developed. The trauma should be considered as a precipitating or aggravating factor and the arteriosclerosis as the predisposing cause of the patient's present condition. Though the actual mechanism is not clear, yet a definite clinical connection between trauma and effect is present.

Case 9. H. B., a 46-year-old male, had always been in good physical health until he sustained an accident on January 12, 1937. He slipped and fell striking the left chest and breast against the sharp corner of a machine. He experienced a great deal of pain and was unable to catch his breath for some time. From that time on

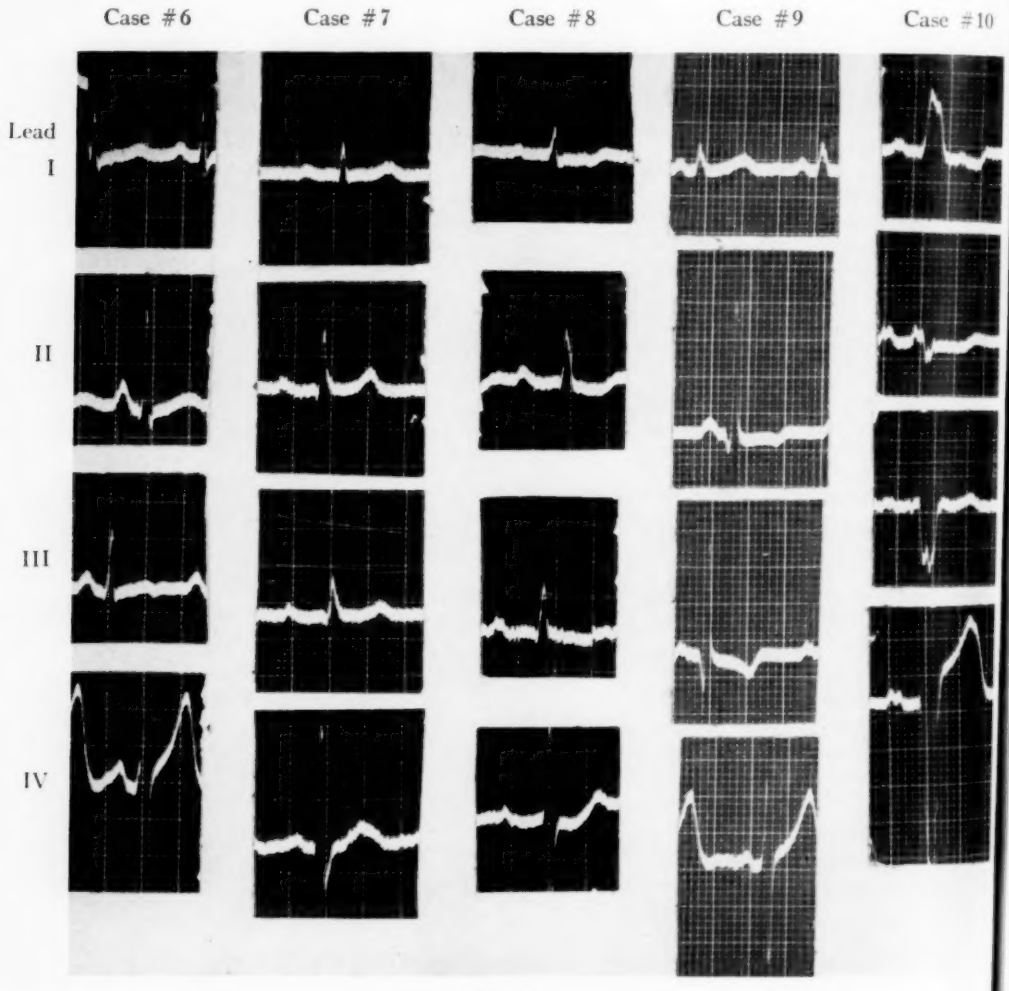

FIG. 3

the patient was heart conscious and complained of precordial pains and some shortness of breath particularly after physical exertion. These symptoms continued intermittently, were progressive in nature and five months later culminated in the complete collapse of the patient caused by an accentuation of the above symptoms. He was institutionalized with a diagnosis of coronary thrombosis. The electrocardiogram showed an inverted and coved T_2 and T_3 associated with a Q_2 and Q_3.

The heart was normal in size and shape. The sounds were of fair quality but somewhat distant. Normal sinus rhythm was associated with a rate of 86, and a short systolic murmur was heard over the apex. The first apical sound was equal

in intensity to the second and the second aortic was greater than the second pulmonic. The roentgenogram was essentially normal and the electrocardiogram showed myocardial damage with residual signs of a posterior coronary occlusion.

Comment: This patient was well until he sustained a direct trauma to his chest. Cardiac symptoms then began and persisted until he collapsed with a coronary occlusion five months later. In trying to reconstruct the picture only the possibilities can be indicated. The heart may have been traumatized and a small area of hemorrhage resulted. This vulnerable spot may have been the starting point of his acute episode. On the other hand, a coronary vessel may have first been injured and subsequently became thrombotic. This patient was too young to be considered as an arteriosclerotic without any reservations. It was felt that the injury and the linking symptoms indicated that trauma was the exciting etiological factor.

Case 10. H. G., was a 50-year-old male, with a history of a coronary thrombosis in 1933. After his recovery he had been able to carry on without any marked impairment of cardiac function. On February 24, 1938, his nose was fractured and a bilateral hematoma resulted. Immediately after this injury pains developed in the chest and the pulse became very rapid. He experienced difficulty in carrying on his routine activities and complained of the precordial distress.

The heart was enlarged to the left; the sounds were of poor quality and lacked the characteristic normal snap. A soft systolic blow was present over the apex. The second apical sound was louder than the first and the second aortic was greater than the second pulmonic. The blood pressure was 120 mm. mercury systolic over 80 mm. diastolic. Roentgenographic studies were essentially normal. The electrocardiogram showed myocardial damage, a typical bundle branch block and residual signs of an anterior coronary closure. These findings were essentially the same as in 1933.

Comment: It was necessary to evaluate the results of a single trauma in a known cardiac. The trauma was directed to the nose and face and produced an increase in the subjective symptoms of the patient. It is reasonable to suppose that the injury only produced an aggravation of the subjective symptoms without any objective changes.

Discussion

Incidence: No accurate statistics are available concerning the frequency of cardiac damage which follows direct nonpenetrating injuries of the chest. In a previous investigation of this subject heart damage was demonstrated in two out of a group of six chest injuries.[17] Through the courtesy of Dr. Thomas A. Gonzales, the chief medical examiner of the City of New York, studies were undertaken to determine the frequency of acute cardiac damage following fatal automobile accidents. The protocols of 50 non-selected and consecutive cases were examined, and in eight (16 per cent) definite macroscopic findings of damage were demonstrated as listed below. (These cases are to be reported at a later date.)

A. One case—rupture of all the heart chambers.
B. One case—a tear of the tricuspid valve extending into the auricle and involving the mouth of the superior vena cava.
C. Five cases—showed subendocardial hemorrhage in the left ventricle and, in some, associated hematomas of the heart muscle and the pericardium.
D. One case—acute dilatation of the left ventricle.

Though this experience is too limited for any definite conclusions, yet it can be stated that direct nonpenetrating injuries of the chest can and do produce heart damage in a fair number of instances. An awareness of the clinical concept is necessary for the proper diagnosis.

Sex: All the patients in this group were males. In the large series collected by Bright and Beck [7] and in those examined at the Medical Examiner's office a fair number of females were encountered. The predominance of the male is probably due to the greater physical exposure of that sex.

Age: The youngest patient was 13 and the oldest 66. In the older group more serious and lasting damage usually followed.

Predisposing Factors: In the experimental laboratory,[12, 13, 14, 16] it has been demonstrated that artificially diseased hearts tolerate less trauma than healthy organs. This has also been observed at the bedside and in order to evaluate any given case it is necessary to consider the previous health of the organ involved. In this small group an underlying latent condition was demonstrated or suspected in eight out of the 10 patients.

Cases 1 and 3. Normal.
Case 2. Healed rheumatic endocarditis.
Case 4. Questionable polycythema vera and coronary sclerosis.
Cases 5 and 6. Latent syphilis.
Cases 7, 8 and possibly 9. Coronary arteriosclerosis.
Case 10. Coronary sclerosis and thrombosis.

Pathology: In the nonpenetrating and non-fatal injuries our understanding of the pathological findings which may result rest primarily on the laboratory work of Moritz and Atkins, Bright and Beck, Schlomka, Kulbs and Strauss. The lesions are usually single or multiple hematomas of the heart and its coverings, which are associated with microscopic and macroscopic lacerations and subendocardial hemorrhages. It is interesting to note that this type of injury may damage the superficial coronary arteries and produce signs of infarction or give rise to subsequent cardiac symptoms (case 9). The experimental work stresses the disturbances of function and this to a great extent finds a parallel at the bedside.[18, 19, 20, 21, 22] This latter aspect of functional disturbances can be best demonstrated by an analysis of the 25 animals which were used by Moritz and Atkins.[16]

a. Eight animals—no change.
b. Five animals—extra systoles

c. Two animals—tachycardia.
d. Seven animals—ventricular fibrillation.
e. Three animals—cardiac standstill.

The pathological changes to a great extent are predetermined by the underlying state of the heart and the trauma often acts as a precipitating or exciting cause. This fact can readily be illustrated by a list of the diagnoses in this series.

Case 1. Contusion and hematoma of the myocardium and possibly pericardium.
Case 2. Healed rheumatic endocarditis, contusion of the heart with moderate loss of function.
Case 3. Contusion of the heart, nodal extra systoles, cardiac neurosis and effort syndrome.
Case 4. Coronary thrombosis.
Case 5. Luetic aortitis and myocarditis, aneurysm of the first portion of the aorta.
Case 6. Luetic myocarditis and aortitis.
Case 7. Myocarditis and first stage heart block, possible coronary thrombosis.
Case 8. Chronic myocarditis and cardiac decompensation.
Case 9. Coronary thrombosis and angina pectoris.
Case 10. Chronic myocarditis, bundle branch block, loss of cardiac function.

Any type of chest trauma may focus the patient's attention on the heart and give rise to cardiac neurosis [28] or the so-called effort syndrome (see case 3).

Trauma: All the patients (except case 10) sustained a direct nonpenetrating trauma of the chest. This injury varied from the standpoint of quality, quantity and location. In some cases the offending force was applied to the precordium with external signs of trauma (cases 2, 4, 7 and 9). In the rest the injury was applied elsewhere on the chest and without external signs. These findings are in accord with the work of Bright and Beck [7] and the work done at the Medical Examiner's Office. How trauma acts on the chest to produce, precipitate or aggravate a heart lesion cannot always be explained satisfactorily. An enumeration of certain facts may help in understanding the mechanism involved:

1. The heart is not a firmly imbedded organ, but on the contrary is free and attached at its base by the large vessels. This anatomical fact allows the heart to be thrown violently against the bony structures of the chest or else torn at its attachment and thus damaged.

2. A hollow viscus which is distended and under pressure is more liable to be damaged by an injury than a similar organ which is relaxed. During systole the heart wall is under tension and trauma at that moment may rupture or damage this organ.

3. In young chests the heart actually may be compressed between the sternum and spine.

4. Immediately preceding an injury the patient automatically fixes the chest in inspiration by closing the glottis and thus produces an excellent medium for the transmission of trauma from the chest wall to the internal viscera.

5. Sudden increases in the intravascular pressures may force the blood back into the heart with sufficient force to damage the endocardium and other layers of the heart. In the postmortem material which was studied subendocardial hemorrhages were found only in the left heart suggesting that a sudden back pressure was capable of producing this lesion.

6. The amount and type of heart damage depends upon the quality and quantity of the trauma.

7. Trauma may be the activating factor in initiating potential disease.

8. One or a combination of these factors may act to produce heart damage.

Clinical Considerations: Experimental and clinical observers have demonstrated that direct nonpenetrating injuries of the chest can produce fatal and non-fatal damage to the heart. In determining the clinical rôle of trauma it would be ideal if heart studies could be obtained before and after an injury. Unfortunately, this is impossible and it is necessary to draw conclusions after damage has occurred.

The past cardiac status of the patient can be determined by careful direct questioning. In medical-legal cases the history as obtained by the first examiner should be given the greatest weight, inasmuch as the stories of some patients change as time goes on, especially with the aid of unethical legal and medical guidance.

In this group the past histories were essentially normal except in cases 2 and 10. The former had a healed rheumatic lesion with no impairment of function and the latter a previous attack of coronary thrombosis. All the patients except case 10 gave a history of a direct nonpenetrating injury of the chest.

Objective and subjective signs of cardiac damage appeared immediately after the injury, except in case 8 who was bedridden. This point is worth stressing, since the subsequent appearance of heart trouble without bridging signs or symptoms would weaken the possibility of a traumatic origin. The subjective symptoms depend to a great extent on the kind of damage and the associated loss of function. Pain, shortness of breath, exertional heart consciousness were the most common complaints.

The objective findings, particularly in the laboratory, would be encountered more often if the possibility of traumatic heart damage would be kept in mind. In case 1 there was an increase in the size of the heart, distant sounds, the presence of a tick-tick rhythm, a failing pressure and changing electrocardiograms. These findings to a lesser degree were also

present in case 2. In the others the underlying condition dictated the resulting clinical picture.

The disability of any patient depends on the functional and structural damage, and occasionally, as in case 3, only a dysfunction results. The prognosis is an individual problem and depends on the type of damage.

Conclusion

1. Direct nonpenetrating injuries of the chest are capable of producing cardiac damage.
2. This has been demonstrated at the bedside and in the laboratory.
3. The diagnosis of traumatic heart damage depends upon:

a. The awareness of this clinical possibility.
b. The history of a direct nonpenetrating injury to the chest.
c. A previous normal cardiovascular history.
d. The appearance of signs, symptoms or laboratory findings indicating heart damage and appearing in the great majority of the cases immediately after the injury and persisting thereafter.

4. In a fair percentage of patients there is usually a quiescent, underlying pathological process such as arteriosclerosis, hypertension, syphilis, blood dyscrasias, rheumatic infections, etc., which may dominate the clinical picture after such an injury.
5. Trauma may aggravate a known cardiac lesion.

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THE TREATMENT OF DIABETES MELLITUS WITH A FOUR-MEAL DIET: A MEANS OF CIRCUMVENTING CERTAIN DIFFICULTIES ARISING IN THE USE OF PROTAMINE ZINC INSULIN *

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New therapeutic agents, like new servants, are apt to present their best sides first, and only upon longer acquaintance reveal the disagreeable traits which hinder their usefulness. Despite technical refinements and improvements in the uniformity and stability of the new insulin products, which culminated in the development of protamine zinc insulin, frequent failings of the slower acting insulins have become apparent with extended experience. Briefly, these failings were manifest in diurnal glycosuria, in the necessity for supplementary injections of regular insulin, in serious, even fatal, reactions, and often, in fact, in such erratic diabetic control as to force the abandonment of protamine zinc insulin in many cases where its aid would have been most welcome.

So manifold are the advantages of this new product, however, that, were it not for the annoying obstacles frequently encountered in its application, protamine zinc insulin would be today the most successful and popular therapeutic resource at the command of every physician who treats diabetes.

We present here our experience with a simple regimen through which we were able to circumvent the usual obstacles. Our method is essentially a departure from the standard three-meal diabetic diet schedule. We have initiated, instead, a modification of the diet so as to provide optimum glucose absorption in relation to the action of protamine zinc insulin. Since the distinctive physiologic property of protamine zinc insulin is its slow absorption, which produces the maximum depression of the blood sugar level some 10 to 24 hours after its injection, it seemed rational to make available an adequate supply of carbohydrate at the time of its greatest need (i.e., coincident with the lowest blood sugar levels). The essence of our program, therefore, was the provision of a liberal carbohydrate meal late in the evening, with the objective of furnishing a store of carbohydrate that would be fed into the blood stream during the night, *slowly and continuously*. This method, it will be demonstrated, stands in contradistinction to the ordinary practice of furnishing a bit of quickly absorbable glucose late in the evening as a precaution against nocturnal reactions.

We found that the four-meal procedure yielded smooth and relatively

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rapid diabetic control, even in severe cases, and has in our experience successfully averted the most disagreeable features formerly encountered with the use of protamine zinc insulin. Diurnal glycosuria was apparently more readily controlled; nocturnal reactions were avoided; the need for supplementary regular insulin was obviated; the simplicity of management with protamine zinc insulin alone was gained. Since our original experience with the controlled cases here presented we have used the new regimen in all patients who are taking protamine zinc insulin. We present at this time this preliminary report of our methods and results with representative diabetic patients of various ages and with different degrees of the illness, in the hope that a more intensive trial by other observers will thereby be stimulated.

Brief Review of Pertinent Literature

The early reports on the use of protamine insulin which appeared in 1936 were, on the whole, uniformly favorable.[1, 2, 3] Yet, at that time, Allen[4] alluded to the annoyances he had encountered with the new product. Later, Joslin,[5] Lawrence and Archer,[6] and others[7, 8, 9] pointed out the difficulties that detract from the simplicity of diabetic control with protamine zinc insulin. It is noteworthy that after two years of trial there is a consistent note of discouragement in the reports, notably in the recent papers of Ralli,[10] and of Boyd and their co-workers,[11] which emphasize only the disappointing features of protamine zinc insulin and the difficulties connected with its use. The actual danger connected with the use of protamine insulins, i.e., the danger of fatal reactions, has only recently been stressed in the pointed editorial warning which appeared in the Journal of the American Medical Association.[12]

Primarily, protamine insulin was introduced to simplify treatment, i.e., to provide one injection daily instead of the three or four that had been required with the use of regular insulin. Experience has indicated, however, that a single daily dose of the new, slow-acting protamine zinc insulin very often failed to control glycosuria, particularly after meals, and that one or more supplementary doses of quick-acting, regular insulin were required for adequate control. The necessity of only one additional dose would have offered no great handicap. In many cases, however, two or three supplementary injections of ordinary insulin were required. Sindoni,[13] having observed that the slow-acting insulin was far inferior to the older product in the prevention of postprandial glycosuria, concluded that protamine insulin itself was inadequate for diabetic management, and should, therefore, be prescribed only as an aid to regular insulin. Obviously, an increased number of injections, instead of simplifying the life of the diabetic, actually makes it more complicated.

Another obstacle frequently encountered with the use of protamine zinc insulin was inferior control of the diabetes. This fault was inherent in the

delayed action of the newer product. The single morning dose of protamine zinc insulin has been found to maintain its action over a period of 24 to 72 hours, oxidizing little glucose within the first four to six hours, but exerting its peak effect (i.e., of depressing the blood sugar level) some 10 to 24 hours after administration. Sprague and his associates [3] at the Mayo Clinic, as well as Mosenthal,[8] and others have demonstrated that protamine insulin had little discernible effect upon the blood sugar level during the day of its injection, whereas it frequently produced hypoglycemia during the ensuing night. As a consequence, sugar was spilled during the day rather than at night. This is just contrary to what had happened with the administration of ordinary insulin in divided doses, with which daytime glycosuria was generally adequately controlled by each mealtime dose of insulin, while nocturnal glycosuria was not readily controlled for lack of available insulin action. Allen,[4] in 1936, indicated this contrariness of control with the new preparation. Since then most workers with diabetes have become familiar with the paradox of protamine action: *sugar spilling by day; hypoglycemic reactions by night.*[4, 7, 10, 11] If the dosage of protamine insulin were increased, hypoglycemic shocks were provoked; if it were reduced, glycosuria became aggravated.[4, 7, 10, 11] So difficult has the problem of diurnal hyperglycemia and glycosuria become that men who had previously considered any glycosuria as evidence of inadequate diabetic control became reconciled to some degree of it with the use of protamine insulin.[3, 9] Others have, indeed, given up the attempt to control difficult diabetics with the new preparation.[10, 11] Although the question of the possible injurious effect of transitory hyperglycemia and glycosuria is still unsettled, it is certainly most desirable to attain complete control, whenever that is possible.

By far the most objectionable feature encountered with the use of protamine zinc insulin was the danger of grave hypoglycemic reactions. Unlike the reactions from ordinary insulin, which came on rapidly after administration, most often during the day, and were quickly controlled by orange juice, the reactions from protamine insulin were insidious in onset, crept on subtly during the night, tended to be prolonged, severe, recurrent, and little or only temporarily influenced by the customary sip of glucose. The gravest peril of the protamine insulin reactions was the nocturnal occurrence of delirium and unconsciousness which have been known to go on unobservedly to sudden death.[12] So ominous were these potentialities of the newer insulin that they were the subject of an editorial warning in the Journal of the American Medical Association [12]—a timely warning, issued during the time of our greatest enthusiasm for this new and generally useful therapeutic agent. The *Journal* reviewed the evidence necessitating this notice and stressed the fact that protamine zinc insulin was not, as some had hoped, a foolproof substitute for the older preparation. The greater hazard of hypoglycemic shock with the use of protamine zinc insulin stood, indeed, as a cogent and valid deterrent to its wider clinical application.

The shortcomings and dangerous potentialities of this most efficacious therapeutic agent offered, therefore, a challenge from the beginning of its use. Several means of avoiding difficulties had been suggested during the first two years of its trial. The original papers of Hagedorn [1] and the earlier papers of Root [2] which referred to this subject advocated the injection of protamine insulin late in the afternoon in order to obtain the maximum insulin absorption during the following day, when its effects would be matched with meals. With this type of administration the Danish originators advised that supper be the smallest meal of the day, and breakfast, the largest. In this country, however, established preference is for the small breakfast, the large supper. In America the earlier practice has been largely supplanted by the morning administration of protamine zinc insulin, both because the afternoon timing failed to prevent nocturnal insulin reactions and because, from the patient's standpoint, it was simpler to have the injection before leaving home in the morning. An added advantage of the morning injection is the fact that its effects are more uniform and better predictable on the smooth nocturnal blood sugar level i.e., when the patient is in the basal condition of rest, than upon the daytime levels, when exercise and other factors produce a widely fluctuating blood sugar content.

As an improved method of preventing nocturnal reactions from a morning dose of protamine insulin, Sprague [3] has suggested that a glass of milk and a few crackers be given before bedtime. We, as well as others, have found this measure valuable, though often inadequate. Rabinowitch has logically advised the use of six feedings a day in order to minimize tendencies to both glycosuria and reactions, but objection to such a regimen comes from the active diabetic, who usually finds the six-meal schedule burdensome. Joslin [14] has recommended that meals be spread further apart over the 12 hours, and that a trifling lunch of 5 to 15 gm. of carbohydrate, perhaps with a little protein, be added in the forenoon, afternoon and at bedtime. The principle demonstrated by this method particularly emphasized the desirability of dietary redistribution as a means of averting trouble, and focused our attention on the late feedings. The more experience we had with protamine zinc insulin, the greater we saw the necessity for large carbohydrate stores at night. We felt, therefore, that the most sustained protection against hypoglycemia would be afforded by a late supper that would be digested and absorbed slowly, while the patient sleeps.

The Four-Meal Diet

Since insulin dosage has always demanded the balancing of insulin action with proper dietary intake, and since, with protamine zinc insulin we were confronted with a new element, i.e., delayed action, it appeared mandatory to arrange a schedule so that absorbed food and slowed insulin action would meet in optimum relationship. We felt that because the greatest protamine insulin effect takes place at night, we should provide a more substan-

tial part of the diet at night. We sought, also, to take advantage of the well established principle that the diabetic patient tends naturally to be worse in the morning, better at noon, and best of all in the evening. Why not, then, furnish an ample meal at the time of greatest carbohydrate tolerance as well as of maximum protamine insulin action? To be most effective, a meal intended to meet the peak action of protamine zinc insulin during the night must perforce be: (1) adequate in carbohydrate content; (2) slowly absorbed so as to feed glucose continuously into the blood stream over a prolonged period; and (3) eaten late enough to be effective throughout the night.

From our previous experience we had found that 5 to 15 grams of carbohydrate, as advocated, were often entirely inadequate to control nocturnal reactions. We had observed several times that although the night snack did control one reaction, it did not prevent the recurrence of reactions later in the night. Behind this failure was the fact that the glass of orange juice or the glass of milk was too rapidly absorbed, too quickly spent. Inadequate protection resulted. These views were well crystallized, in our experience, with the use of protamine zinc insulin by a juvenile patient with rather severe diabetes (case 1), who had for some time impressed us with the necessity of furnishing larger and larger snacks of the diet in the evenings in order to protect him against the violent and recurrent insulin reactions to which he had been subject. Largely on empiric grounds we developed the practice of furnishing one-fifth of his total daily allowance of food in a night feeding. We favored foods in this meal that would be digested and absorbed slowly, yielding glucose not only from the starch, but also from the protein and fat in foods such as eggs, cream and butter. We felt that 9:30 or 10 p.m. was the best time for the fourth meal, inasmuch as that was over four hours after the usual dinner and still more than an hour before bedtime.

With these clinical impressions as a guide, we started on August 18, 1937 to prescribe a four-meal regimen with a *liberal night feeding* for patients who were taking protamine zinc insulin. The total diet prescriptions were the same, in general, as those upon which the patients had been previously maintained. These were calculated to supply the individual's caloric needs. Formerly these patients had taken three meals of approximately equal portions (or of 1/5, 2/5 and 2/5 respectively, according to the individual patient's tastes).

The new four-meal diets were divided as follows:

1/5 of the total caloric intake at 8 a.m.
1/5 at noon
2/5 at 5 p.m.
1/5 at 9:30 p.m.

The prescribed carbohydrate content was, on an average, over 180 gm. The total available glucose from the carbohydrate, protein and fat in the

daily diets of our patients ranged from 166 to 300 gm.; while the total oxidizable glucose in the fourth meal alone was 32 to 53 gm.

A fairly representative 9:30 p.m. feeding consisted of the following foods or their equivalents:

Bread	1 slice
40 per cent cream	50 gm.
Milk	200 "
Eggs (or the equivalent, as meat or cheese)	2

Our more recent experience has indicated that the principle of providing an ample night feeding not infrequently requires further extension, particularly in severe diabetic patients. Thus, when one-fifth of the diet fails to produce perfect control, two-fifths, furnishing a total glucose value of 74 to 104 gm., may be more successful. In four of our cases (1, 6, 8 and 11) the necessity and effectiveness of such an extension are clearly emphasized.

Case Reports

Case 1. R. P., a boy of 18, markedly underweight (81 lbs.–36 kg.), presenting severe diabetes of seven years' duration, was observed over a period of two years. During the control period in the hospital in October 1936, he had proved to be highly refractory to management with protamine insulin, because, while spilling 11 to 28 gm. of sugar in the urine during the day, he suffered on five occasions severe hypoglycemic reactions, marked by violent convulsions and loss of consciousness, during the night. An evening snack of 15 to 20 gm. of carbohydrate had proved inadequate for prevention of the nocturnal reactions.

Throughout the next year he was seen at intervals, and his food allowance was increased periodically to allow for growth. During 1937, he was receiving from 36 to 44 units of protamine zinc insulin. Glycosuria was only poorly controlled. Any attempt to raise the insulin dosage during this period resulted in violent hypoglycemic reactions which could not be eliminated by numerous modifications of the three-meal diet. When the glycosuria was under fair control, he suffered severe nocturnal insulin reactions and their aftermath of morning headaches. When the dose of protamine zinc insulin was reduced to obviate the appearance of hypoglycemic reactions marked glycosuria recurred.

Four-meal regimen: Because of the extremely erratic and generally unsatisfactory level of control it became apparent that a still greater supply of slowly absorbable glucose was needed at night, during the peak of protamine zinc insulin absorption. On August 18, 1937, we therefore began the use of a regular "fourth-meal," providing one-fifth of the total caloric intake at 9:30 p.m., instead of three standard meals, supplemented by a glass of milk at bedtime. The regimen was later modified to furnish fully one-third of the total daily calories (total available glucose 45 gm.) in the night feeding. With the institution of the new dietary arrangement management at once became simplified. With the modified diet an initial dose of 56 units of protamine zinc insulin was given in the morning. The continued presence of "loaded" sugar reactions in collections of all the urine samples demanded an increase in the dosage. The morning dosage of protamine zinc insulin was, therefore, increased gradually until at one time 100 units of protamine zinc insulin were attained, at which time all samples of urine in the 24-hour period became negative for sugar. Blood sugar levels which, at the beginning of treatment with the four-meal diet, ranged between 153 to

295 mg. per 100 c.c. of blood, at various times of the day, descended to levels of between 70 to 111 mg., with complete control of the diabetes, within two weeks.

The most instructive feature of this case was the fact that the large dose of protamine zinc insulin required for control was, with the four-meal diet, tolerated without provoking any insulin reactions. The smoothness and rapidity with which control of the diabetes was achieved with the new regimen was in striking contrast to our experience in the treatment of this boy previously with the more usual forms of diabetic management. At the time of writing he has gained considerable carbohydrate tolerance and is being maintained in perfect diabetic control with 80 units of protamine zinc insulin daily.

Case 2. K. G., a white female, 57 years old, weighing 140 lbs. (63 kg.) had been treated for diabetes in the outpatient clinic for two years. This was the second case to demonstrate the value of a fourth meal. She was admitted to the Montefiore Hospital for the treatment of acute lumbosacral sprain November 8, 1937. During her stay she continued her usual three-meal diabetic diet (see chart), with which she received 40 units of protamine zinc insulin. Glycosuria (7–14 gm. sugar per 24-hour specimen) occurred during the first 10 days, while the fasting blood sugar level ranged within normal limits. The protamine zinc insulin dosage was gradually increased to 58 units, and a slice of bread with a glass of milk from the noon feeding was ordered for 9:30 p.m. The glycosuria diminished to 5 gm. daily, most of the sugar loss taking place in the afternoon and evening. The fasting blood sugar remained at 107 mg. Later the original dietary prescription was further rearranged so as to furnish one-fifth of the total daily calories (total available glucose 58 gm.) in the 9:30 p.m. feeding. During the following week all of the 24-hour samples tested negative for sugar, and the fasting blood sugar levels remained normal. Since her discharge from the hospital she has continued on the four-meal regimen and has reported regularly to the outpatient clinic for over a year. She has remained controlled, has maintained her weight, has required smaller doses of protamine zinc insulin, being controlled on 40 units daily.

Case 3. Mrs. E. G., aged 66, had been under regular observation at the diabetic clinic of the Montefiore Hospital for three years prior to her admission February 19, 1938, for treatment of hypertrophic arthritis of one knee. In the clinic she had almost constantly a moderate degree of glycosuria concurrent with fasting blood sugar levels of 100–110 mg. per 100 c.c. Upon admission she was maintained on her customary diet of carbohydrate 225 gm., protein 75 gm., fat 90 gm., divided about equally among three meals. Her usual dosage of 50 units of protamine zinc insulin daily, supplemented by 20 units of regular insulin at 8 a.m., was also prescribed. Because of an insulin reaction on the morning of February 21, the regular insulin was discontinued. For several days she presented a mild degree of glycosuria (1 gm. in 24 hours), predominantly in the 6 p.m. sample. On February 23, blood sugar determinations at 8 a.m., 11 a.m., and 4 p.m. were 101, 165 and 102 mg. per 100 c.c. of blood, respectively. At 2 a.m. of the following night she suffered an insulin reaction marked by tremor and profuse sweating. She left the hospital March 4, 1938.

Because of another severe attack of arthritis she was readmitted to the hospital March 30, 1938. The daily diet prescription was left unaltered, except that the food was distributed at that time into four meals, allowing one-fifth of the total dietary intake at 9:30 p.m. This redistribution was made in the desire to circumvent the recurrence of insidious insulin shocks in a woman of her age. With the modified regimen and 45 units of protamine zinc insulin no glycosuria appeared in the 24-hour specimen during the next two weeks. On only two occasions were there traces of sugar in single, afternoon voided specimens. The fasting blood sugar on April 14 was 136 mg. At no time during this hospital stay did any insulin reactions occur. She was discharged April 14, 1938, and has reported periodically to the outpatient

TABLE I

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.				Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	P	F	Total Oxidizable Glucose, gm.					
1 (R. P.)	16	M.	On 3-meal Oct. 1936 to Aug. 1937	150	90	99	210	1850					Prot. zn. insulin 58 u. + soluble insulin 10 u.	Average 20–40 gm. daily	Frequent and severe with loss of consciousness. Gen. nocturnal	3 wks. in hospital	Had been receiving 15 gm. glucose as orange juice 10 a.m., 3 to 9 p.m. daily with 3-meal diet. Average fasting blood sugar levels 60 to 90 mg. while on 3-meal diet.
	18 years at this period	→	On 4-meal Aug. 1937 to Apr. 1939	225	95	170	310	2810	75*	31	38	103	80 u. protamine zinc insulin only	Less than 5 gm. usually 24 hr. sample sugar-free	None in 20 months	2 wks. in hospital	Diet had been increased to allow for growth and greater physical activity. At one time took 100 u. prot. zn. insulin for control without provoking reactions. Av. fasting blood sugar levels 100 to 130 mg. on 4-meal diet.
2 (K. G.)	57	F.	On 3-meal Jan. 1937 to Nov. 1937	250	70	90	299	2090					Protamine zinc insulin 40 to 55 u.	7–14 gm. daily	None	Never entirely sugar-free	Complained of hunger on 3 meals. Fasting blood sugar levels usually elevated (180 to 220 mg.).
			On 4-meal Nov. 1937 to Dec. 1938	...	...	sam	e..	....	40†	15	15	50	Protamine zinc insulin 40 u.	None or less than 5 gm. in 24 hr.	None	10 days in hospital	No longer hungry. Slow gain in weight. Maintained excellent control during out-patient attendance 1 year. Fasting blood sugars 86–95 mg.
3 (E. G.)	66	F.	On 3-meal Apr. 1937 to Mar. 1938	225	75	90	278	2010					Prot. zinc insulin 45 to 50 u. + soluble insulin 20 u.	"Loaded" 24 hr. specimen	Several early morning. Three severe nocturnal shocks	Never entirely sugar-free	Coincidental hypertrophic arthritis. Periods of weight loss. Fasting sugar levels 100 to 160 mg.
			On 4-meal Apr. 1938 to Apr. 1939	...	...	sam	e..	....	44	14	17	54	Prot. zinc insulin only. 40 u.	None or "sl. trace"	None in 12 months	5 days in hospital	Weight maintained. Diabetic control well-maintained over 1 year. Fasting sugar levels 130 to 150 mg.

* 1/3 of total allowance.
† Sl. less than 1/5.

TABLE I—*Continued*

TABLE I—*Continued*

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.				Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	P	F	Total Oxidizable Glucose, gm.					
4 (R. M.)	42	F.	On 3-meal Apr. 1936 to May 1938	175	75	120	232	2080					50 to 80 u. daily Prot. zinc insulin	"Loaded" 24 hr. specimen	None	Never entirely sugar-free	Severe diabetes; loss of weight. Received also 15 gm. carbohydrate as milk every evening, in addition to 3 meals. Low fasting blood sugars 94 to 97 mg.
			On 4-meal May 1938 to Apr. 1939	160	70	111	211	1919	31	14	21	42	Prot. zinc insulin 40 u.	None or faint-trace	None	1 week in hospital	Operation for cervical polyps. Controlled with individual doses soluble insulin during post-operative days only. Four meal diet resumed after 5 days. Weight gained.
5 (S. M.)	68	F.	On 3-meal Sept. 1937 to Apr. 1938	200	65	100	248	1960					Prot. zinc insulin 40 u.	Gen. "Loaded" 24 hr. specimen 4 to 8.5 gm.	None	Not completely in 8 months	Diabetic and arthritic out-patient Wass. ++++. Elderly and arteriosclerotic. Blood sugar levels av. 150 to 200 mg.
			On 4-meal Apr. 1938 to Apr. 1939	. . .	. . .	sam	e . .	. . . .	37	14	19$_4$	46	Prot. zinc insulin 15 u.	Consistently sugar-free 24 hr. samples	None	9 days hospital	Because of improvement under anti-arthritic therapy, became more active physically; required less insulin. Gained weight. Fasting blood sugars usually 140 to 150 mg.
6 (W. Mc.)	72	M.	On 3-meal June 1935 to June 1938	195	65	106	243	1994					Prot. zinc insulin 40 u. + soluble insulin 15 u.	8 to 30 gm. daily	Several	Not sugar-free	Senile; diabetes of 3 yrs. duration. Auricular fibrillation (recent). Gangrenous ulcer of foot (recent). Received orange juice 9 p.m. (10 gm. carb.).
			On 4-meal July 1938 to Aug. 1938	150	70	100	200	1780	57‡	25	40	74	Prot. zinc insulin only 40 u.	Almost entirely sugar-free 20 days	None	5 days in hospital	During hosp. control fasting. Blood sugar levels 85 to 163 mg. Spread of gangrene; patient refused operation. Died.

‡ 2/5 of diet.

TABLE I—*Continued*

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.				Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	P	F	Total Oxidizable Glucose, gm.					
7 (R. F.)	57	F.	On 3-meal Mar. 1938 to Apr. 1938	175	75	88	223	1800					Prot. zinc insulin 35 u. +	13 to 25 gm.	Several severe nocturnal	Sugar not controlled	Entered hospital presenting severe glycosuria, acetonuria. Arteriosclerotic. Blood sugar level 190 to 240 mg.
			On 4-meal May 1938 to Apr. 1939	...	...	same	...	...	34	14	17	42	Prot. zinc insulin 35 u.	None	None	10 days in hospital	Fasting blood sugar levels 90 to 140 mg. Gained weight.
8 (M. B.)	40	M.	On 3-meal (3 weeks)	(Approximately 2900) Home care									Variable prot. zinc insulin + regular insulin trial	Severe 20 to 30 gm. in first few days of hospitalization	None	Not controlled prior to hospitalization	Entered hospital in severe state of acidosis. Loss of 40 lbs. (18 kg.) in 3 weeks prior to admission. Diplopia; pains in legs.
			On 4-meal July 1938 to Mar. 1939	200	75	190	260	2800	80§	30	70	104	Prot. zinc insulin only 32 u.	None	None	10 days in hospital	Very simply controlled. 4-meal diet used from start. Blood sugar levels 92 to 113 mg. Returned to hard physical labor and maintained weight and strength.
9 (R. L.)	46	F.	On 3-meal May 1936 to Aug. 1938	160	70	115	208	1950					Prot. zinc insulin 10 u.	Gen. "Loaded"	None	Never quite sugar-free	Diabetic out-patient. Had lost 40 lbs. (18 kg.) in weight in first 2 yrs. of illness. Complained frequently of hunger 1 hr. after meals.
			On 4-meal Aug. 1938 to Apr. 1939	...	...	same	...	...	32	14	23	42	Prot. zinc insulin 6 u.	None or faint trace	None	3 wks. dispens.	Gaining weight. Blood sugar levels 144 to 170 mg.

§ 2/5 of diet.

TABLE I—*Continued*

TABLE I—*Continued*

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.				Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	P	F	Total Oxidizable Glucose, gm.					
10 (M. M.)	66	F.	On 3-meal May 1937 to Aug. 1938	200	65	100	247	1960					Prot. zinc insulin 24 to 32 u.	"Trace" to "Loaded"	None	—	Diabetic out-patient. Poor coöperation because of hunger between meals. Fasting blood sugars range 185 to 233 mg.
			On 4-meal Aug. 1938 to Apr. 1939	. . .	. . .	sam	e . .	. . . .	40	13	20	49	Prot. zinc insulin 25 u.	None or o. c. "trace"	None	4 wks. dispens.	Satiety with diet; better coöperation. Fasting sugar levels 130 to 150 mg.
11 (F. S.)	50	F.	On 3-meal 1933 to July 1938	140	55	60	176	1320					Soluble insulin 20–0–20 u. Later prot. zinc insulin 40 u.	"Trace" to "Loaded" 24 hr. specimen	None	—	Diabetic out-patient. Blood sugar levels 295 to 350 mg. Attempt at abrupt change from soluble to prot. insulin provoked nausea, anorexia, loss of weight and increased glycosuria.
			On 4-meal July 1938 to Apr. 1939	160	65	60	204	1440	32	13	12	40	Prot. zinc insulin 50 u.	None	None	5 wks. dispens.	Gaining weight. Fasting blood sugar levels 95 to 160 mg.
12 (L. M.)	67	F.	On 3-meal 1935 to July 1938	120	60	120	166	1800					Soluble insulin 15–0–15 u. Later prot. zinc insulin 20 u.	Traces to "Loaded" 24 hr. specimen	None	—	Diabetic out-patient: markedly under weight; arteriosclerotic; chronic bronchitis; hunger a frequent complaint. Fasting blood sugar range 230 to 275 mg.
			On 4-meal July 1938 to Apr. 1939	. . .	. . .	sam	e . .	. . . .	24	12	24	33	Prot. zinc insulin 30 u.	None or occ. trace	None (10 months)	6 wks. dispens.	No reaction in spite of increased protamine insulin dosage required for control, although patient is markedly arteriosclerotic. Gaining weight. Fasting blood sugars 160 to 180 mg. Satiety with 4 meals.

TABLE I—*Continued*

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.				Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	P	F	Total Oxidizable Glucose, gm.					
13 (M. L.)	56	F.	On 3-meal June 1938 to Aug. 1938	150	60	18	187	1000					—	"Loaded" 24 hr. specimen	None	—	Obese, but had lost 40 lbs. (18 kg.) within two months of onset of diabetes. This case the only low caloric diet in series. Blood sugar levels 230 to 250 mg. in a.m.
			On 4-meal Aug. 1938 to Apr. 1939	. . .	. . .	sam	e . .	. . .	30	12	3.5	37	Prot. zinc insulin 20 u.	—	None	6 days in hospital	Acetone and diacetic acid negative. Satiety on low caloric, 4-meal diet. Fasting blood sugar levels 120–162 mg.
14 (N. N.)	42	M.	No (3-meal control)										—	15 gm. in 24 hrs. on admission	—	—	Untreated diabetes for 1 yr., complicated by coronary-sclerosis. (Case included to illustrate value of starting control with 4-meal regimen.)
			On 4-meal Aug. 1938 to Apr. 1939	195	80	95	251	1950	39	16	19	49	Prot. zinc insulin 35 u.	None	None in 9 months	9 days in hospital	Fasting blood sugars 100 to 130 mg. Rapid control of diabetes with 4-meals. Safety (no reactions) in presence of coronary sclerosis through use of protective fourth meal.

department since. Continuing the four-meal regimen and the use of 40 units of protamine zinc insulin daily, the patient has remained under good diabetic control and free from insulin reactions. The excellent control achieved with the four-meal regimen is a striking contrast to the former control period (with three meals), during which diurnal glycosuria alternated with frequent nocturnal reactions.

Case 4. Mrs. R. M., a severe diabetic, aged 42 years, had been treated in the outpatient clinic for two years. Prior to 1938 she had required 80 units of regular insulin with a 2080 calorie, three-meal diet for control. In February 1938, she was placed on protamine zinc insulin, requiring 80 units every morning. In the evenings, at 9 p.m., she received 200 gm. of milk (carbohydrate value 15 gm.) from her dietary allowance. Since her transfer to protamine zinc insulin, she had presented, almost daily, moderate to severe glycosuria, while, at the same time, her morning blood sugars were low (94–97 mg. per 100 c.c.). On May 13, 1938 she was admitted to the hospital to undergo vaginal hysterectomy for uterine polyps. At this time a 1920 calorie diet was prescribed, consisting of carbohydrate 160 gm., protein 70 gm., fat 111 gm., divided into three meals and a night allowance of milk, as described. She received 50 units of protamine zinc insulin daily. Glycosuria persisted, while the fasting blood sugar levels were low. The diet formula was, therefore, rearranged into four meals, furnishing one-fifth of the food at 9:30 p.m. (total glucose value 45 gm.), while the protamine zinc insulin dosage remained unchanged. Within several days the urine became entirely sugar-free and remained so.

On June 4, 1938, the patient was operated upon, under gas anesthesia. During the immediate postoperative period (five days) soluble insulin only was used in doses indicated by the degree of glycosuria. By June 10, when the patient was again able to take her full four-meal diet, the use of protamine zinc insulin was resumed and was gradually reduced to 35 units daily, which fully controlled the glycosuria and kept the fasting blood sugar at a normal level. For the remaining period of hospitalization all samples of urine were negative for sugar. She was discharged June 16, 1938. Periodic check-up during the next eight months indicated that the patient remained well controlled, maintained her weight, was using only half the dose of protamine zinc insulin (40 U.) that had been required previously to maintain a normal blood sugar level with the same caloric intake.

Case 5. S. M., a colored female, aged 68, diabetic and arthritic, was observed for years in the outpatient clinic. She was maintained on a 1960 calorie diet, together with 40 units of protamine zinc insulin daily. Review of her record for the past eight months showed that as a rule she presented marked glycosuria at each clinic visit. She was admitted into the hospital April 9, 1938. Her dietary prescription was modified into a four-meal distribution, the total glucose value of the 9:30 p.m. feeding being 46 gm. The urine became regularly sugar-free when a daily morning dose of 22 units of protamine zinc insulin was attained, and she remained aglycosuric for the remaining 20 days in the hospital; the fasting blood sugar level was maintained at approximately 160 mg. She was discharged from the hospital May 20, 1938. Under appropriate therapy, her arthritic symptoms were relieved and she became more active physically, consequently requiring less insulin during the eight months following her discharge. At the time of writing she required only 15 units of protamine zinc insulin daily, was free of glycosuria, and the fasting blood sugar level was 145 mg. per 100 c.c. of blood. Most apparent benefit of the smaller, more efficiently utilized insulin dosage was the minimal risk of provoking dangerous insulin reactions in this elderly patient.

Case 6. W. McC., male, aged 72, was admitted into the Montefiore Hospital June 24, 1938, with diabetes of three years' duration as well as a gangrenous, infected ulcer of the foot, and auricular fibrillation, both of recent onset. Upon admission he was continued on his former diet of 195 gm. carbohydrate, 65 gm. protein, and 106 gm.

fat, divided into three nearly equal meals, except for 10 gm. of carbohydrate which were furnished at 9 p.m. With this diet he required 40 units of protamine zinc insulin, supplemented by a morning dose of 15 units of soluble insulin. Whereas the fasting blood sugars were normal on this regimen, glycosuria was severe, ranging from 8 to 30 gm. daily. In spite of the glycosuria occasional reactions appeared. When the carbohydrate allowance was gradually reduced by 40 gm. and soluble insulin omitted considerable diurnal glycosuria still persisted.

We felt that since hypoglycemic reactions might prove disastrous to a person of his age and myocardial status, they should be avoided, if at all possible. On July 1, 1938, his regular dietary allowance was redistributed into a four-meal regimen which provided the greatest supply of food, i.e., fully two-fifths of the total allowance in the 9 p.m. feeding. The total glucose value of the night feeding was 45 gm. The protamine zinc insulin dosage of 40 units daily was maintained. During the following 20 days practically all urine specimens tested negative for sugar, while the fasting blood sugar level varied from 85–163 mg. By July 22, 1938, the patient required only 35 units of protamine insulin for control. (Subsequently, the gangrene of the foot spread, the patient refused operation, and died August 7, 1938.)

Case 7. Mrs. R. F., aged 57, was referred for control of recently discovered diabetes. She entered the hospital April 20, 1938, presenting marked glycosuria, acetonuria, and a fasting blood sugar level of 200 mg. per 100 c.c. of blood. Her diet consisted of carbohydrate 175 gm., protein 75 gm., fat 88 gm., in three meals. With this diet she required 35 units of protamine zinc insulin for partial control of glycosuria. With this dosage, or even less, she suffered several nocturnal insulin reactions. The diet was, therefore, rearranged into four meals, providing a total glucose allowance of 42 gm. at 9:30 p.m. daily. The protamine zinc insulin dosage remained at 35 units. Subsequent to this change she was free from reactions. She was discharged from the hospital May 13, 1938, and was advised to continue on the four-meal regimen. In the ensuing nine months she has had no reactions, has gained 10 lbs. (4.5 kg.) in weight, has had no glycosuria, and her fasting blood sugars have remained at normal levels.

This case well illustrates what often occurs in the attempted management of a diabetic patient with protamine insulin and the use of a standard three-meal diet i.e., just when the glycosuria is beginning to disappear hypoglycemic reactions set in. The dual rôle of the fourth meal, other conditions remaining the same, is well demonstrated in this case.

Case 8. M. B., aged 40, a steel worker engaged in heavy physical work, complained of pains in the legs, difficulty with vision, and loss of 40 lbs. (18 kg.) in weight within the three weeks prior to his examination, and was found to be suffering from acute, severe diabetes. He entered the Montefiore Hospital July 10, 1938 in a state of severe acidosis, for the control of which protamine zinc insulin plus soluble insulin was used. The prescribed diet contained 200 gm. carbohydrates, 75 gm. protein, 190 gm. of fat, divided into four meals. After four days of treatment there was still an excretion of 12 gm. of sugar in the urine for a 24-hour period, but the fasting blood sugar fell to 81 mg. The night (9 p.m.) allowance of food was, therefore, increased from one-fifth to two-fifths of the day's total. There was no need for supplementary regular insulin within two days after this change, a morning dose of 45 units of protamine zinc insulin alone sufficing for adequate control. The urine specimens for six days prior to discharge were uniformly sugar-free, while the fasting blood sugar levels ranged from 113 to 134 mg. Within 16 days of admission the patient was discharged from the hospital entirely sugar-free. During the following nine months, back at his regular hard work, he required, with a continued four-meal regimen, only 32 units of protamine zinc insulin to maintain uniformly perfect control of his diabetes.

From previous experience we feel that with the standard three-meal regimen and protamine insulin the management of this case would have been one fraught with many difficulties i.e., persistent glycosuria, reactions, the necessity of repeated supplementary injections of regular insulin in addition to the protamine zinc insulin, recourse to supplementary feedings, and a longer period of hospitalization until control was finally achieved. With the four-meal regimen as a recourse, the zig-zag course of constantly varying food and insulin prescriptions previously demanded in such cases appears to have been obviated.

Case 9. Mrs. R. L., aged 46, observed in the outpatient clinic, had lost considerable weight in the past two years, coincident with the onset of diabetes. With a 1930 calorie diet of three meals, and a matutinal dose of 10 units of protamine zinc insulin, the fasting blood sugar level dropped to 147–160 mg. per 100 c.c. of blood. She presented considerable glycosuria, however, especially in the afternoon and evening specimens. She was troubled, besides, by hunger one hour or so after lunch, and more frequently after supper. On August 1, 1938 a four-meal division of her previous diet was instituted, furnishing one-fifth of the calories at 9:30 p.m. The protamine zinc insulin dosage was unchanged. Since this alteration, the 24-hour specimens of urine have become entirely sugar-free. Exceptionally, a trace of sugar appeared in single afternoon samples. She has no longer been troubled with hunger, has been content with her feedings, and has gained four lbs. (1.8 kg.) on her new regimen. At the time of writing her diabetes is perfectly controlled with only 6 units of protamine zinc insulin.

Case 10. Mrs. M. M., an ambulatory diabetic patient in our clinic, aged 66, had been under observation for 16 months, during which period she was taking a 1960 calorie, three-meal diet, together with 24 to 32 units of protamine zinc insulin daily. The fasting blood sugar levels had been in the proximity of 200 mg. throughout this period, while the 24-hour urine sample almost invariably showed sugar in amounts varying from traces to loaded specimens. This patient, we knew, frequently deviated from her diet by nibbling between meals. She has been observed periodically for a period of nine months since she started on the four-meal diet, has been observed to be more content with the prescribed feedings, and hence more coöperative. There has been considerable improvement in the control of the diabetes, as well as in the patient's morale. The urine has remained consistently sugar-free, the fasting blood sugar levels have dropped to 130–150 mg.; the amount of protamine insulin required has been 30 units.

Case 11. Mrs. F. S., 50 years old, has attended the diabetic clinic since 1933. In previous years, with a 1320 calorie diet, she had required soluble insulin in the dosage of 20–0–20 units for moderately good control. An attempt early in 1938 to change from regular insulin to 40 units of protamine zinc insulin while on a three-meal diet resulted in a break of control. She lost almost 10 pounds within two weeks and spilled considerable sugar. On July 10, 1938, the patient was placed on a four-meal regimen (1440 calories) of carbohydrate 160 gm., protein 65 gm., fat 60 gm., together with an initial dose of 35 units of protamine zinc insulin daily. Marked glycosuria persisted. The dosage was gradually raised to 60 units of protamine zinc insulin and was well tolerated without reactions.

Traces of sugar, at first present after the change, disappeared within several weeks. Periodic check-up over a period of nine months after the change to the four-meal regimen revealed no sugar in the 24-hour specimens of urine, fasting blood sugars of 88 and 90 mg. per 100 c.c. of blood, and a gain in weight of three lbs. (1.5 kg.). At the time of writing, the patient required only 50 units of protamine zinc insulin daily for control.

A period of poor control, such as is represented in this case, is frequently encountered upon making the change from soluble insulin to protamine zinc insulin of

the same dosage. This occurs because each meal is no longer oxidized by the direct, immediate action of a meal-time dose of soluble insulin, but by the delayed and variable action of protamine zinc insulin given in the morning. Previously, this eventuality would have been met by adding supplementary regular insulin at each meal. The simpler alternative, illustrated in this case, is to lop off some of the food from breakfast, lunch and dinner, in order to provide a night meal that is readily utilized at the height of protamine zinc insulin action. We feel that without the four-meal diet, providing a protective night meal, this patient might not have tolerated, without serious reactions, the 60 units of protamine zinc insulin required for control.

Case 12. L. M., 67 year old colored female, has attended the diabetic clinic since 1935. During the period of management with soluble insulin she had received 15–0–15 units, but presented frequent periods of glycosuria (generally nocturnal), and fasting blood sugar levels ranging from 178 to 295 mg. From November 1937 to July 1938 she received an 1800 calorie, three-meal diet, with 20 to 30 units of protamine zinc insulin. Upon this regimen, while she spilled less sugar than formerly (generally in the afternoon and evening specimens), she maintained a high fasting blood sugar level (260 mg.). On August 17, 1938, she was ordered a diet of higher caloric value (2100 calories), divided, however, into four meals. She was maintained on 30 units of protamine zinc insulin daily. Within two weeks the patient achieved the best diabetic control that she had presented in three years, and has remained controlled until the time of writing.

This case illustrates the difference in problems offered by the old insulin and the new. In the days when quick-acting, regular insulin was administered with meals, sugar was controlled by day, spilled by night. With slow-acting protamine zinc insulin sugar was spilled during the day, since the new insulin did not attain its maximum effect until night. In view of this peculiarity of the newer insulin, a fourth meal was given at night and was efficiently utilized. This change resulted in the best diabetic control that this patient had enjoyed in three years of treatment.

Case 13. M. L., a 56-year-old female, was admitted to the Montefiore Hospital because of a recently discovered diabetes of approximately two months' duration. She was obese, but stated that she had dropped in weight from 245 pounds (111 kg.) to 203 pounds (92 kg.) coincident with the onset of symptoms of diabetes two months before. On a 1000 calorie diet, containing carbohydrate 150 gm., protein 60 gm., and fat 18 gm., divided into four meals, and with 20 units of protamine zinc insulin daily, the urine specimens which had been loaded with sugar for the first three days, became negative, except for one 24-hour period, four days before discharge, when 6.4 gm. of sugar were spilled. Thereafter, 24-hour collections of urine remained consistently sugar-free. Two fasting blood sugar determinations taken prior to the four-meal dietary plan were 238 and 254 mg. per 100 c.c. of blood, respectively, while those taken after the change were 162, and, on the day of dismissal, 129 mg. Perfect diabetic control having been established, the patient was discharged within one week after admission to the hospital, and has remained sugar-free since.

Case 14. N. N., a salesman, 42 years of age, was admitted to the Montefiore Hospital for control of previously untreated diabetes of one year's duration. He also presented a history of one attack of severe angina pectoris three years previously, attributable to coronary sclerosis. On admission, he spilled 15 gm. of sugar in a 24-hour collection of urine, and his fasting blood sugar level was 250 mg. per 100 c.c. of blood. A diet of 1950 calories, containing carbohydrate 195 gm., protein 80 gm., and fat 95 gm., divided into four meals, was prescribed. One-fifth of the daily food allowance was given at 9:30 p.m. With the daily administration of 35 units of protamine zinc insulin the 24-hour specimens of urine became sugar-free and the fasting blood sugar reached a level of 129 mg. per 100 c.c. of blood. Control of the diabetes was attained on the ninth day of hospitalization. At no time have insulin

reactions, particularly dangerous in the presence of coronary sclerosis, occurred. Diabetic control has been well maintained over an eight-month period of observation.

Results

Fourteen illustrative cases, which have been observed closely on the four-meal regimen, form the basis of this preliminary report. Ten of these had been under observation for *control periods* of one to six years prior to the institution of the new dietary arrangement, and hence afford a suitable basis of comparison. Our youngest patient was 18 years of age; the rest were from 40 to 72. Ten were women, four men. One was obese; two were well below the average weight for their height and age. Twelve of the patients were engaged in active occupations, including those of student, steel-mill laborer, and housewife. These patients were all maintained on relatively high carbohydrate diets (average over 180 gm.) both before and after the four-meal arrangement. All cases received, during their entire periods of observation, protamine zinc insulin in doses ranging from 10 to 100 units daily; several had received supplementary doses of soluble insulin in the earlier phases of their treatment. Criteria of improvement were based upon an evaluation of the individual patient's course, as previously noted, compared to that after use of the four-meal regimen, both periods being adequately checked by frequent blood sugar studies, urine test and weight records.

Our experience with these cases was uniformly favorable, and indicated that the four-meal regimen offered a means of circumventing the most objectionable features connected with the use of protamine zinc insulin. We feel that this regimen now enables us to realize in practice the simplicity of management originally expected from the use of the new insulin. Because we were able successfully to control even the most severe diabetics in this group with only one injection of protamine zinc insulin daily, we have not used supplementary doses of soluble insulin since. The results to date confirm our original experience with this preliminary group. The five patients in this series who had required one or more daily doses of soluble insulin previously, required none after the institution of the new feeding schedule (cases 1, 3, 6, 8, and 11); nor did they require food between meals to balance the action of such supplementary injections. Protamine zinc insulin was used more efficiently with four meals than with three, hence in six cases (2, 3, 4, 5, 6, and 8) a reduction in the daily amount of protamine insulin required was made possible. In our present practice we feel that the four-meal regimen allows the most convenient type of diabetic therapy since the advent of protamine zinc insulin.

Because of previous difficulties in attaining good diabetic control with the new product, some workers had concluded that the use of protamine zinc insulin was not compatible with the maintenance of physiologic levels of the blood sugar. Boyd,[11] for example, has reported that, in diabetic chil-

dren, a lower level of control resulted from the use of protamine zinc insulin. We have found the reverse to be true with the use of the four-meal diet in adults. Not only was the blood sugar in these controlled cases maintained at lower, more normal levels than before, but there was an absence of the wide fluctuations which had previously been observed with the standard three-meal program. With the four-meal regimen we no longer face the problem of glycosuria by day, hypoglycemia by night.

Contrary to the experience of Mosenthal,[8] Ralli,[10] and others who found that patients requiring over 50 units of insulin daily were difficult or impossible to control with the use of the new insulin, our experience with several cases that had previously required 50 to 80 units of protamine zinc insulin daily was that these severe diabetics achieved and maintained excellent diabetic control with the four-meal regimen and a single daily injection of protamine zinc insulin (cases 1, 2, 3, 4). Although our cases were not those of juvenile diabetics, it is possible that the principle of this regimen might be applicable with a similar degree of success in juveniles also. Diabetic control, once achieved, has been maintained over periods varying from six months (minimum) to over one year of observation. It is our opinion that a higher level of control, rather than the opposite, has been made possible by the use of protamine insulin, if combined with the four-meal diet.

The greatest benefit derived from the new regimen was the effective prevention of nocturnal insulin reactions through the use of the *protective fourth meal.* It will be observed from the chart that several patients (cases 1, 3, 6, 7) who had previously suffered repeated hypoglycemic reactions while on a three-meal regimen, or a three-meal regimen with a snack (15 gm. carbohydrate) at bedtime, suffered none on the four-meal regimen which furnished 30 to 50 gm. of carbohydrate at 9:30 p.m. This was true even of our youngest, most severe diabetic, who required 100 units of protamine zinc insulin daily. The nocturnal and fasting blood sugar levels were, on a whole, above the hypoglycemic levels that had previously been encountered with the use of protamine insulin. Even the patients who received over 40 units daily remained free of reactions. Significantly, the patient taking at one time 100 units (case 1) suffered not a single reaction while on the four-meal diet. Since smaller doses of protamine zinc insulin were generally necessary after adoption of the new dietary habit, less hazard of hypoglycemia existed. Since the use of supplementary soluble insulin had been made unnecessary the danger of diurnal shocks was likewise minimized. It is significant that even in those cases where the dietary formula and the protamine zinc insulin dosage remained unchanged, redistribution of the food to provide a night meal at the height of the delayed protamine insulin action sufficed to prevent violent nocturnal reactions.

Because one-fifth or even two-fifths of the total diet was furnished at night, even elderly, arteriosclerotic patients were able to utilize protamine insulin without fear of reactions or the risk of a fatality (cases 3, 5, 6,

10, 12). No reactions occurred in our series of cases throughout the entire period of observation during the new regimen. The protective value of the "fourth meal," as compared with the evening snack of carbohydrate as more generally employed, appears to be established.

We anticipated some difficulty with the new regimen since it involved a radical change in the patients' fixed habit patterns of three meals. We found, however, that diabetic patients as a rule, actually prefer a bite—usually more than a bite—in the evenings. The subjective response of the patients was gratifying. They felt satiated at meal times. They were more content and, therefore, more coöperative, on four feedings. Most of the patients had previously received multiple injections of insulin daily. Now they welcomed the simplified procedure of using one injection daily, and were encouraged by their improved blood sugar and urine reports. Almost every patient in the series maintained his weight or gained while on the four-meal regimen; none lost. No one has objected that the evening feeding was burdensome or impractical; on the other hand, none voiced preference for food between meals as previously given. The four-meal arrangement has proved particularly popular with our clinic patients. We rather believe, from the general improvement of that group, that dietary infractions were negligible in comparison with previous experience.

The gains achieved by the new four-meal regimen are reflected in the changed attitude with which we ourselves now approach the control of a new diabetic with protamine zinc insulin. The new regimen engenders a feeling of confidence regarding "difficult" cases. Patients with severe diabetes, who previously would have been recalcitrant to management with protamine zinc insulin, no longer appear as formidable problems, since we now have some assurance that we can safely, and in short order, raise the protamine insulin dosage until glycosuria is controlled, *without the usual danger of insulin reactions.* We know that any tendency toward nocturnal hypoglycemia will be prevented by the absorption of one-fifth or two-fifths of the daily carbohydrate allowance (even more if the occasion should warrant) from an evening feeding. Case 8 is particularly illustrative of a severe diabetic patient who was brought under excellent control with the four-meal regimen in about half the time that we had formerly required with similar cases. Such saving of time constitutes a great economic advantage to patient and hospital alike.

Patients with mild diabetes offer no great problem under the four-meal regimen. Our experience suggests that it is possible to use protamine zinc insulin in the treatment of mild diabetes safely and successfully in the office or clinic, with little or no necessity for hospital admission.

Comment

In the clinical use of protamine insulin we were confronted with a new situation in the treatment of diabetes mellitus. With its use we were forced

to sacrifice the exactitude with which we could previously balance a given amount of carbohydrate in an individual meal with a suitable dose of soluble insulin. But this disadvantage is more than offset by the many conveniences offered by the newer product. Protamine insulin, properly used, furnishes a physiologic reservoir of insulin in the body. Up to the present our command over this reservoir has not been as complete as we might wish. It would undoubtedly be highly desirable to have a type of insulin, the action of which would be uniform and sufficiently prolonged to oxidize glucose throughout the day. Until such a product is perfected, however, we must resort to several other expedients in order to obtain safe, yet effectual, results with the use of protamine zinc insulin.

The trouble with protamine zinc insulin has been that a dose just sufficient to control diurnal glycosuria frequently proved inadequate to control hyperglycemia. If that dosage was increased, reactions occurred; if it was decreased, supplementary soluble insulin was required to control spilling of sugar during the day. Aside from the inconvenience, a constant danger is present with the use of added doses of soluble insulin, namely, that the patient is apt to get a double action of insulin—first, from the quick acting soluble dose; second, from the slowly liberated protamine insulin—at the great risk of reactions. Supplementing the diet with snacks between meals for the prevention of such diurnal reactions is a complicated, and frequently unsatisfactory expedient. We have not found it necessary to use feedings between meals, yet we encounter no diurnal reactions with the use of the four-meal regimen. In present diabetic management, as in standard management of peptic ulcer, frequent feedings are demanded; the advantageous distribution of these feedings is of the greater importance in diabetes.

Our suggestion, simply stated, is this: since, with a single injection of protamine insulin, we can no longer place insulin action precisely at those points around the clock where the food is, we can, with a high factor of safety, place food where the greatest insulin action is.

Conclusions

In order to obtain the maximum efficiency with the use of protamine zinc insulin, a four-meal regimen of diabetic management, including a liberal food allowance late in the evening, was instituted. Whereas the daily dietary formulae were those common in modern diabetic practice, including high carbohydrate diets, the *distribution* of food was such as to provide the greater absorption of glucose at the time of the greatest absorption of protamine zinc insulin.

A series of 14 controlled cases is presented, illustrating the basis of our present use of the four-meal diabetic regimen, from which we conclude:

1. The four-meal regimen affords the utmost simplicity of diabetic treatment. A single daily injection of protamine zinc insulin suffices for

control. Neither supplementary doses of soluble insulin nor feedings between meals are necessary with this regimen.

2. Smoother, quicker, more adequate control of diabetes is made possible, even in severe cases, with minimal doses of protamine zinc insulin.

3. The grave danger of hypoglycemic shock, and hence the possibility of insulin fatalities, are eliminated by the use of a " protective fourth meal."

4. The satiety, contentment, and morale of diabetic patients are enhanced by the use of four meals daily.

5. The four-meal regimen makes the treatment of diabetes mellitus with protamine zinc insulin a safe and practical procedure for office and clinic use.

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ROENTGEN TREATMENT OF THE ADRENAL GLANDS IN ANGINA PECTORIS (ONE HUNDRED CASES) *

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A NEW THEORY OF ANGINA PECTORIS

THE typical occasions on which angina pectoris complaints occur, namely physical exertion, cold temperature and psychic emotion are physiologically connected with discharges of adrenalin from the suprarenal medulla as has been demonstrated in animals by Cannon [1] and his co-workers, and in man by Meythaler and Wossidlo.[2]

The specific effect of adrenalin upon the metabolism of the heart muscle consists essentially of a marked increase in local oxygen consumption (Barcroft and Dixon,[3] Evans and Ogava,[4] Gremels,[5] Rein,[6] etc.). This exceeds by far the intensity of oxidation which is required to meet the needs of the increased hemodynamic action and does not coincide with it (Gollwitzer-Meier, Kramer and Krüger [7]).

According to the same authors the increase of myocardial oxygen consumption following the administration of adrenalin is much greater than the simultaneous increase of coronary blood flow in the denervated heart of the dog:

	Increase of O_2-consumption of the heart muscle	Increase of coronary blood flow
30 sec. after 0.01 mg. adrenalin	+ 251%	+ 46%
45 sec. after 0.01 mg. adrenalin	+ 190%	+ 77%

In the innervated heart similar reactions take place, although to a minor degree. Accumulation of lactic acid in the heart muscle due to shortage of oxygen under the influence of adrenalin has been observed by Weicker,[8] Gottdenker and de Marchi,[9] etc.; histological myocardial changes of the anoxia type have been described by Franz,[10] Veith [61] and others after injections of adrenalin.

The explanation of angina pectoris sensations as being caused by a shortage of oxygen and formation of anoxybiotic acid metabolites within the heart muscle due to "coronary insufficiency" (Keefer and Resnik [11] and others) is generally accepted and does not require any further comment.

Gollwitzer-Meier [12] in a recent survey concerning the production of energy by the mammalian heart makes the following remark on the effect of adrenalin: "This sudden increase in oxygen consumption must lead to the danger of tissue anoxia if the increase of coronary blood flow is not an adequate one." It is evident that this will be the case in the presence of arteriosclerotic changes in the walls of the coronary arteries. In considera-

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tion of these facts a theory is advanced that *angina pectoris on effort, on cold, on emotion, etc., is due to an acute anoxia of the heart muscle which is caused by the specific effect of sudden discharges of adrenalin from the suprarenal glands: increase of myocardial oxygen consumption, without adequate dilatation of the sclerotic coronary arteries* (figure 1).

As additional arguments in favor of this theory the following facts can be stated:

1. Subcutaneous injection of adrenalin produces anginal pain fairly regularly in patients with coronary disease but fails to do so in normals (Levine, Ernstene and Jacobson [13]);

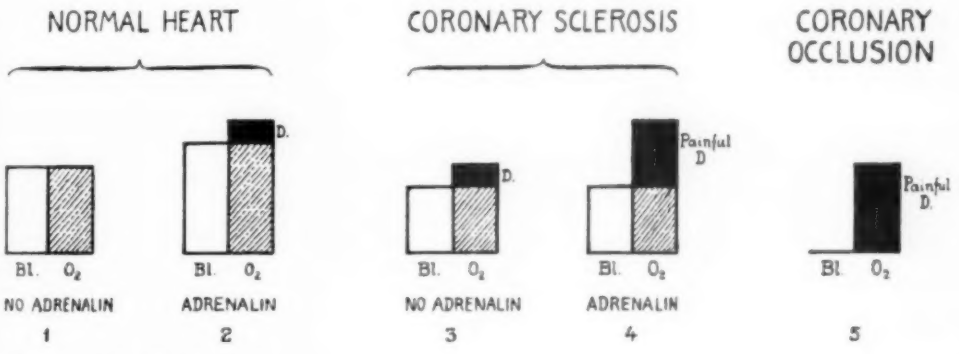
NORMAL HEART
CORONARY SCLEROSIS
CORONARY OCCLUSION
D.
Painful D
Painful D.
Bl. O_2
NO ADRENALIN
ADRENALIN
NO ADRENALIN
ADRENALIN
1
2
3
4
5
Bl = CORONARY BLOOD SUPPLY
O_2 = MYOCARDIAL OXYGEN CONSUMPTION
D. = MYOCARDIAL OXYGEN DEFICIENCY
1 O_2-CONSUMPTION NORMAL - BLOOD SUPPLY ADEQUATE
2 O_2-CONSUMPTION INCREASED - BLOOD SUPPLY ALSO INCREASED, BUT NOT SUFFICIENTLY TO PREVENT A SLIGHT PAINLESS OXYGEN DEFICIENCY
3 BLOOD SUPPLY IMPAIRED - OXYGEN CONSUMPTION NORMAL. THEREFORE A SLIGHT PAINLESS OXYGEN DEFICIENCY
4 O_2-CONSUMPTION INCREASED BUT BLOOD SUPPLY SUBNORMAL. THEREFORE A STRONG OXYGEN-DEFICIENCY AND ANGINAL PAIN.
5 BLOOD SUPPLY LACKING - O_2-CONSUMPTION NORMAL. THEREFORE A STRONG OXYGEN DEFICIENCY AND ANGINAL PAIN.

FIG. 1.

2. In an experiment which I carried out on myself, then at the age of 32, a subcutaneous injection of a large dose of adrenalin (1.3 mg.) resulted in an attack of distressing anginal pain with a typical anoxic electrocardiogram;

3. Inhalation of low oxygen concentrations leads both to discharge of adrenalin (Cannon [1] and others) and in patients with coronary disease to anginal pain (Rothschild and Kissin [14]);

4. Nicotin causes discharges of adrenalin (Cannon, Aub and Binger,[15] Eichholtz,[16] Stewart and Rogoff,[17] Strauss,[18] Short and Johnson [19]) and frequently produces attacks of angina pectoris in patients with coronary sclerosis (Külbs,[20] Denecke,[21] Strauss,[18] etc.);

5. Overdosage of insulin provokes a reactive output of adrenalin from the suprarenal medulla (Brandt and Katz,[22] La Barre and Houssa,[23] Kugelmann,[24] etc.) and is sometimes followed by symptoms of angina pectoris (Hadorn,[25] Schönbrunner,[26] etc.);

6. An increased amount of adrenalin has been found in the blood during attacks of acute arterial hypertension which were accompanied by angina pectoris (Brandt and Katz [22]);

7. Attacks of angina pectoris in patients with tumors of the suprarenal medullar tissue are apt to subside completely after removal of the tumor (Lenhartz,[27] etc.);

8. There is a close similarity of the electrocardiogram after injection of adrenalin (Lepeschkin,[28] Vesa,[62] etc.) and during attacks of angina pectoris (depression of S–T, inversion of T, etc.); both of them being of the anoxia type (Büchner [47]).

9. The iodine level of the blood is increased after injection of adrenalin (Schittenhelm and Eisler,[29] Gutzeit and Parade,[30] etc.), after effort (Gutzeit and Parade,[30] MacCullagh and Roy,[31] Raab and Schönbrunner [32]), on psychic emotion (Schittenhelm and Eisler [29]) and during attacks of angina pectoris (Siedek [33]);

10. Angina pectoris is frequently improved through total thyroidectomy (Blumgart, Levine and Berlin,[34] etc.) which diminishes both the secretion of adrenalin and the response of the sympathetic system to adrenalin (Asher and Nakayama,[35] Oswald,[36] Reiss,[37] Bansi,[38] etc.); accordingly the painful reaction to adrenalin in patients with coronary sclerosis disappears after thyroidectomy (Eppinger and Levine [39]);

11. Roentgen irradiation of the suprarenal glands is followed by a reduction of their ability to produce adrenalin (Eisler and Hirsch,[40] David and Hirsch [41]) and even leads to destructive histological changes of the suprarenals if applied in a large dosage (Cottenot,[42] Tsuzuki,[43] Martin, Rogers and Fischer,[45] Engelstad and Torgersen [46]). Roentgen irradiation has furthermore proved to be a very potent therapeutic means in the treatment of angina pectoris (Raab,[44] Hadorn [25]). It also leads frequently to a partial or complete normalization of the pathological electrocardiogram of patients who have been subjectively improved or entirely freed of their complaints (Raab and Schönbrunner [48]);

12. The rise of blood iodine after effort which is probably due to an adrenalin effect was found diminished or absent in cases of angina pectoris after irradiation of the suprarenal glands (Raab and Schönbrunner [32]).

Against the assumption of an impaired dilatability of the coronary arteries, the objection could be raised, that the pain-relieving effect of nitroglycerin and other nitrites is due, according to general belief, to a dilatation of the coronary arteries. It is, however, not known whether the nitrites exert only a vaso-dilatory effect or whether they do not also diminish the sensitivity of the thoracic sympathetic nerves or the myocardial oxygen con-

sumption or both. Kretz [49] and others have expressed doubts concerning a purely vaso-dilatory mechanism of the effect of nitrites in angina pectoris. Riseman and Brown [50] have observed an analgesic effect of nitroglycerin also in pain of non-cardiac origin.

No definite explanation can be given at present for the not infrequent absence of anginal complaints in patients with severe coronary sclerosis. It seems, however, that besides suprarenal activity a second extra-cardiac factor is essential for the occurrence of stenocardiac pain, namely, an abnormal sensitivity of the thoracic sympathetic nerves (Morawitz,[51] Edens,[59] etc.).

Roentgen Irradiation of the Suprarenal Glands

The therapeutic effect of roentgen irradiation of the suprarenal glands has been studied over a period of two and a half years on one hundred patients with angina pectoris. None of them showed signs of marked cardiac decompensation. The technic of treatment consisted in series of six single treatments on consecutive days; three times on the left side and three times on the right side; each treatment 200 to 250 r, 0.5 mm. Cu plus 1 mm. Al, 180 KV, 4 MA; size of fields 10 by 15 centimeters.

With only very few exceptions all patients were treated outside of the hospital under their habitual living conditions. Most of them were kept under regular control at intervals of two months on an average. In every case an approximate graphic record of the intensity and frequency of anginal complaints was made (figures 2 to 8), the height of the black areas indicating their severity. Every small white square represents one series of irradiations of the suprarenals; the larger ones represent series of irradiations of the chest according to the suggestion of Lian,[52] Gilbert,[53] Sussman,[54] Wasch and Schenck,[63] etc.

As a rule no other treatment was allowed besides the roentgen irradiations except nitroglycerin and some rather ineffective theobromine-luminal combinations (Purartrial, etc.) provided that they had been used before. Only in a few instances which are recorded on the charts, euphyllin preparations or strophanthin or iodine were given for a limited time.

The diagnoses were based on the history and on the description which the patients gave of their typical complaints. Electrocardiograms at rest and after exercise (running up stairs) were recorded in 38 of the cases. Twenty-three of them presented pathological alterations either of an anoxia type (19 cases) or indicating a disturbance of intraventricular conduction. In 20 patients whose complaints suggested the presence of some continuous neuralgic factor besides the typical stenocardiac complaints during exercise, emotion, cold, etc., spinal arthritic changes were detected through roentgen examination of the thoracic spinal column (indicated as "sp." on figures 2 to 8). Four patients (15, 25, 51, 55) had syphilis, one of them (51) with aortic insufficiency. In seven cases (7, 17, 21, 39, 41, 69, 78)

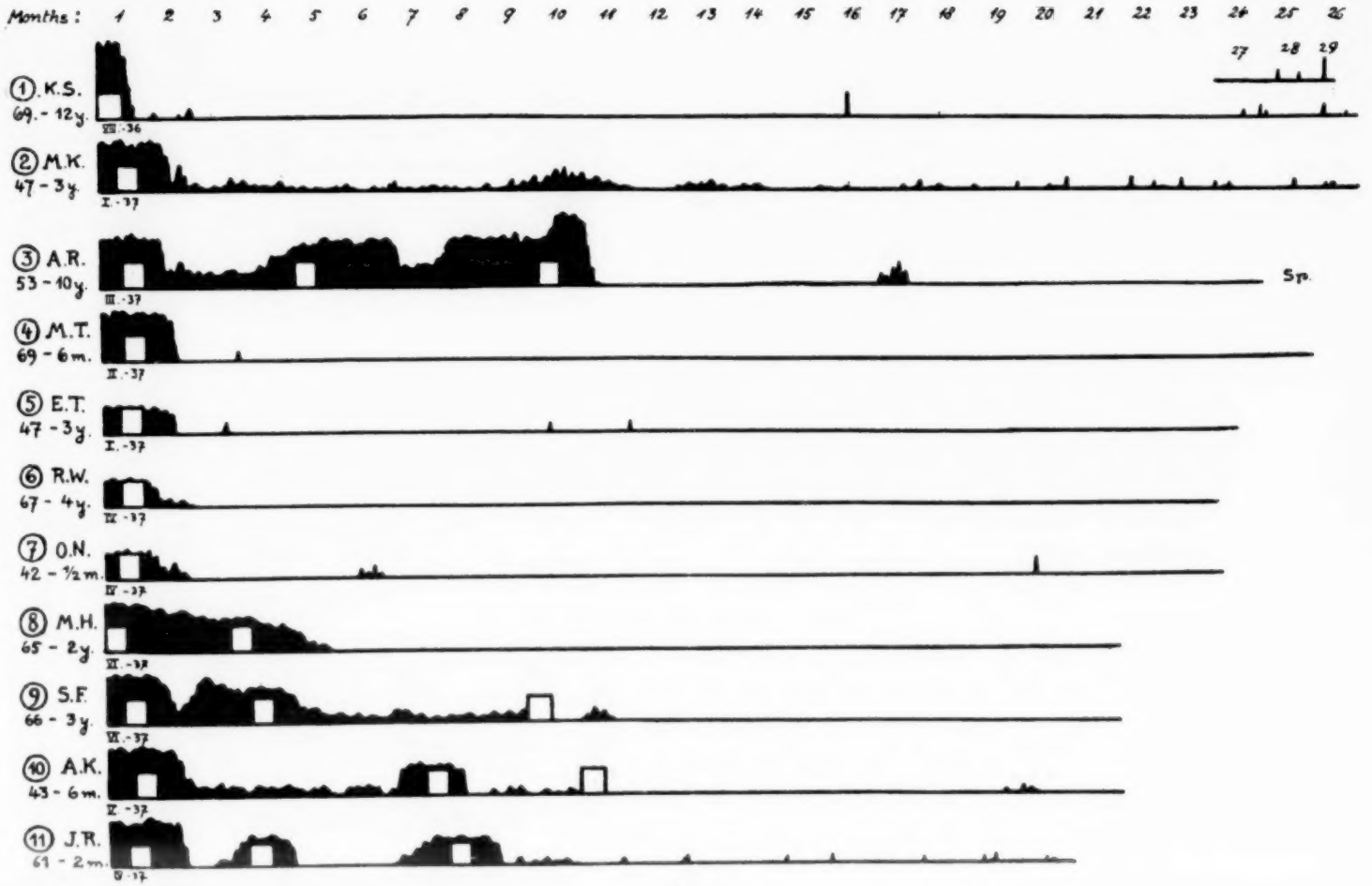
Months: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
① K.S. 69. - 12 y.
XII. 36
② M.K. 47 - 3 y.
I. 37
③ A.R. 53 - 10 y.
III. 37
Sp.
④ M.T. 69 - 6 m.
II. 37
⑤ E.T. 47 - 3 y.
I. 37
⑥ R.W. 67 - 4 y.
IX. 37
⑦ O.N. 42 - ½ m.
IV. 37
⑧ M.H. 65 - 2 y.
XI. 37
⑨ S.F. 66 - 3 y.
VI. 37
⑩ A.K. 43 - 6 m.
X. 37
⑪ J.R. 61 - 2 m.
V. 37

FIG. 2.

FIG. 2.

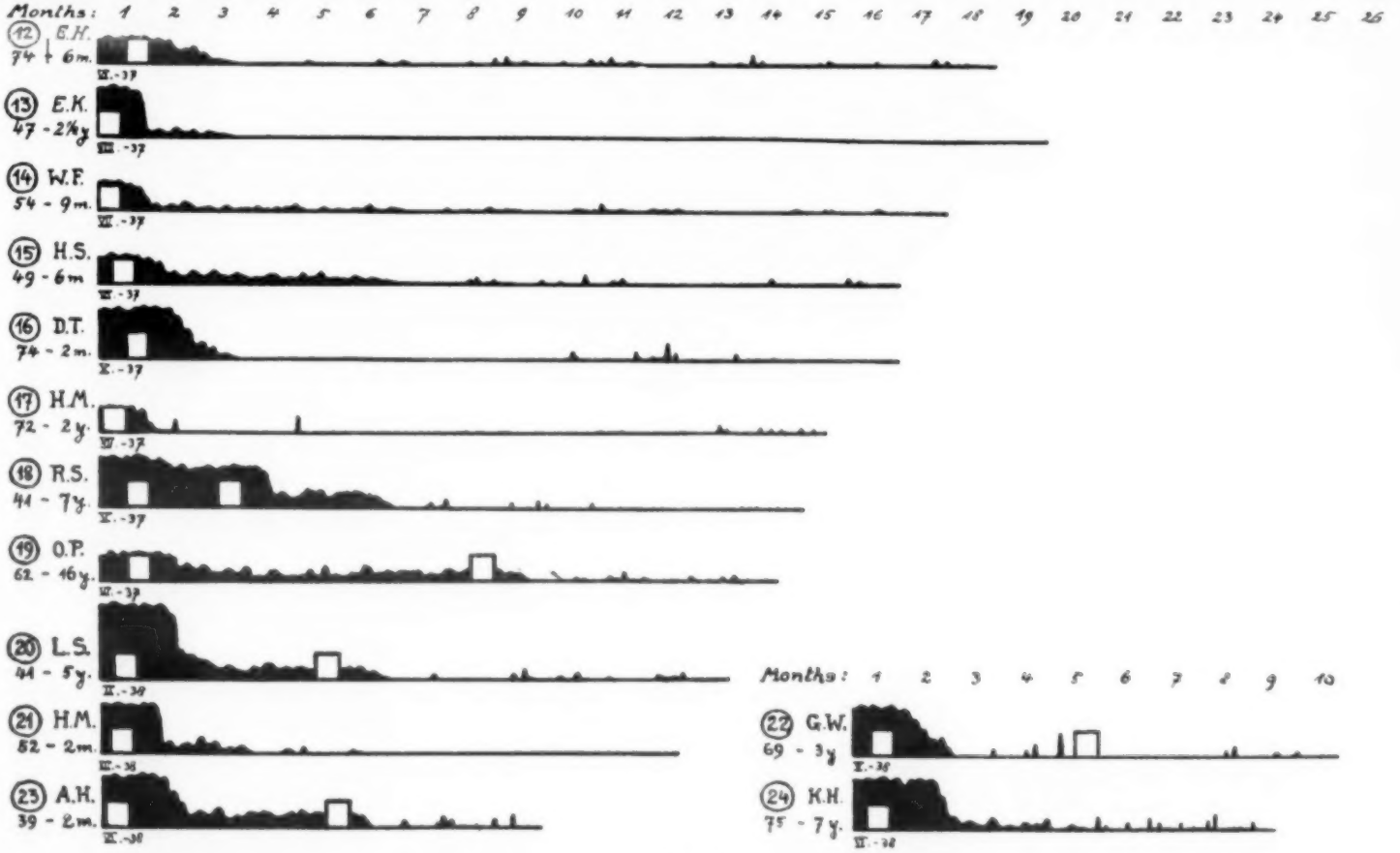
Months: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
(12) E.H. 74 + 6m.
(13) E.K. 47 - 2½y
(14) W.F. 54 - 9m.
(15) H.S. 49 - 6m
(16) D.T. 74 - 2m.
(17) H.M. 72 - 2y.
(18) R.S. 41 - 7y.
(19) O.P. 62 - 16y.
(20) L.S. 41 - 5y.
(21) H.M. 82 - 2m.
(23) A.H. 39 - 2m.
Months: 1 2 3 4 5 6 7 8 9 10
(22) G.W. 69 - 3y
(24) K.H. 75 - 7y.

FIG. 3.

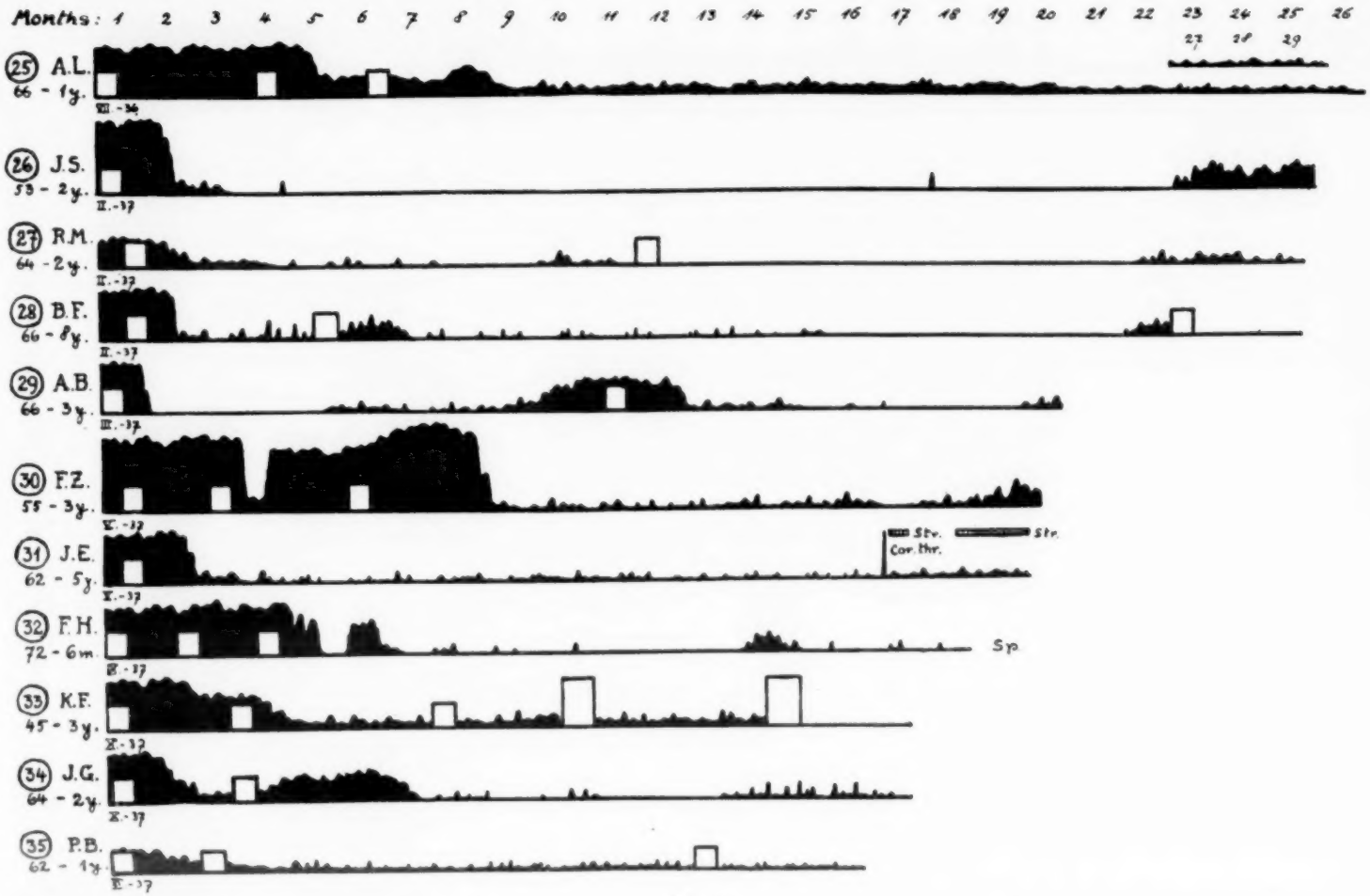

Fig. 4.

Months: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

FIG. 4.

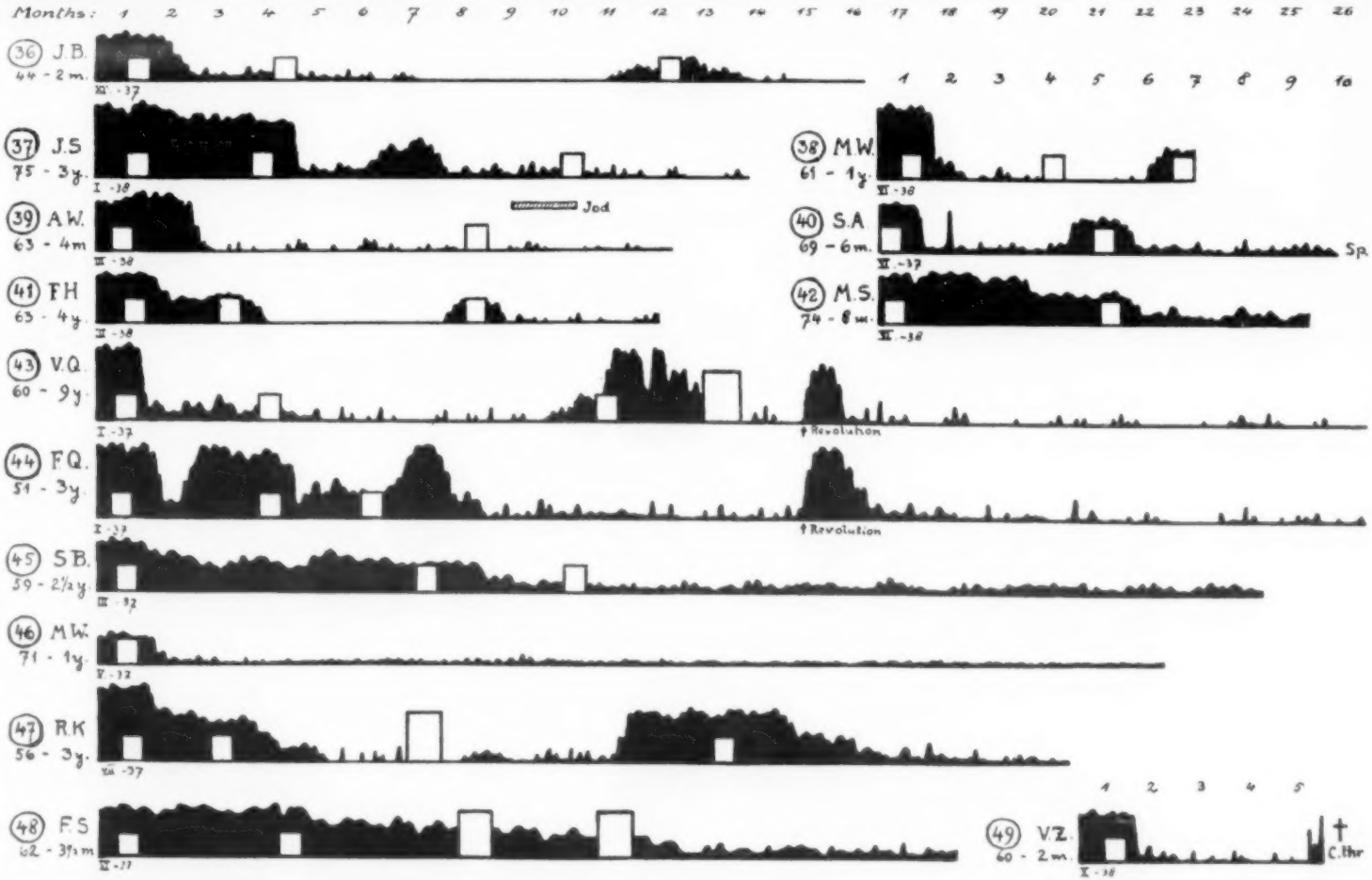
Months: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
36 J.B. 44 - 2 m.
37 J.S. 75 - 3 y.
38 M.W. 61 - 1 y.
39 A.W. 63 - 4 m
Jod
40 S.A 69 - 6 m.
Sp.
41 F.H 63 - 4 y.
42 M.S. 74 - 8 m.
43 V.Q. 60 - 9 y.
† Revolution
44 F.Q. 51 - 3 y.
† Revolution
45 S.B. 59 - 2½ y.
46 M.W. 71 - 1 y.
47 R.K 56 - 3 y.
48 F.S 62 - 3½ m
49 V.Z. 60 - 2 m.
C. thr

FIG. 5.

there had occurred attacks of coronary thrombosis according to the history but no patient was submitted to roentgen irradiation of the suprarenals unless a space of at least several months had elapsed after the last attack. Seventy-five patients were smokers although of different degrees; many of them had ceased smoking soon after the onset of their disease. Fifty-three suffered from stenocardiac pain, not only on effort, etc., but also at rest and at night. Eighty-five per cent of all patients were males.

The duration of the complaints before beginning of roentgen treatment had varied widely between two weeks and 23 years. A great majority of the patients had undergone other treatment before irradiation, mostly without effect or with unsatisfactory result: nitrites, iodine, Padutin, papaverin, combinations of theobromin and barbituric acid, etc. Twenty-eight patients had received euphyllin or analogous preparations and six had been given strophanthin injections. Seventy-three had used nitroglycerin which gave temporary relief in 69 and was ineffective in four of them.

Effect of Irradiations upon Anginal Symptoms

The graphic tracings of the intensity and frequency of stenocardiac complaints before and after roentgen treatment show a complete or almost complete disappearance of the symptoms of angina pectoris for at least three months and up to 28 months in about 40 per cent of the cases. A considerable improvement from at least 6 up to 24 months was noted in about 20 per cent. A moderate improvement from 6 to 17 months was reported in about 15 per cent and no improvement at all in about 25 per cent. The average duration of improvement in the first two groups (+++ and ++) together was 13½ months and in the third group (+) 7½ months.

Irradiation of the chest was added to that of the suprarenals in 18 cases in which the latter alone seemed to be insufficient or not at all effective. In six of them it apparently caused a further improvement, probably due to a diminution of intrathoracic nervous sensitivity as it has been assumed by Gilbert [53] and others.

The patient's own judgment is in most of the cases the only standard to be used in evaluating the therapeutic effect of any treatment in angina pectoris. For this reason I sent inquiries to those patients who could still be located during the first months after my departure from Europe (December 1938) in order to complete their history. Among 60 answers which I received there were 48 statements of a persisting satisfactory condition or of further improvement. Two patients reported recent relapses. Two of my oldest patients who had been bed-ridden for years before the roentgen treatment, because of daily frequent severe attacks (numbers 1 and 43) were almost completely free from pain for a total period of 28 and 20 months respectively. They could walk and climb stairs without discomfort. Patient 3, a merchant, who according to his own statement "had not been able to do the easiest kind of work before the treatment" has now applied for

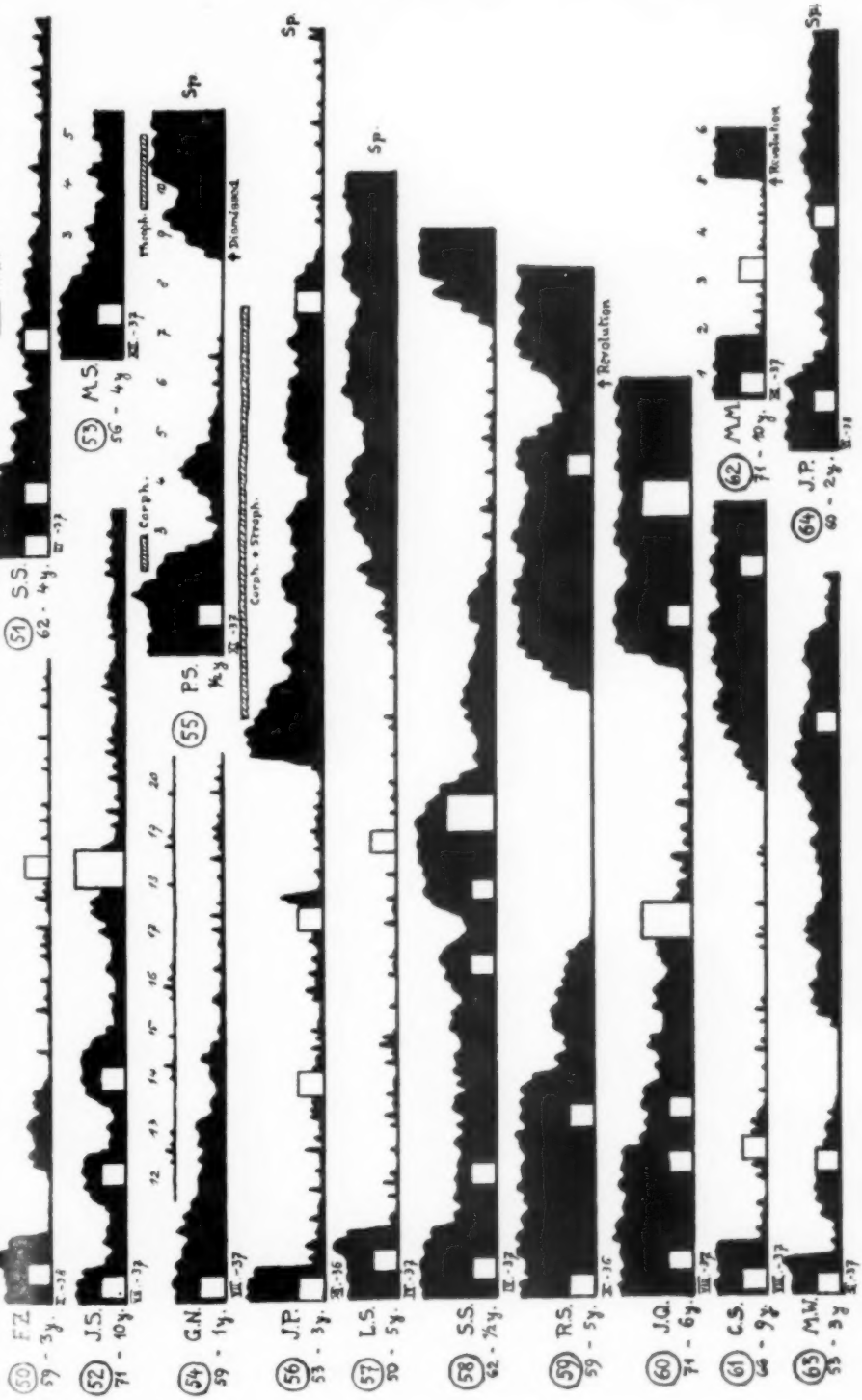
50 F.Z. 59 - 3y. X-34
52 J.S. 71 - 10y. XI-33
54 G.N. 59 - 1y. XII-37
56 J.P. 53 - 3y. X-36
57 L.S. 50 - 5y. IX-37
58 S.S. 62 - ½y. IX-37
59 R.S. 59 - 5y. X-36
60 J.Q. 71 - 6y. III-37
61 C.S. 66 - 9y. III-37
63 M.W. 53 - 3y. X-37
55 P.S. 4½y. X-37
51 S.S. 62 - 4y. XI-33
53 M.S. 56 - 4y. XII-33
62 M.M. 71 - 10y. XI-37
64 J.P. 60 - 2y. X-37
Sp.
Revolution
Diarrhoea
Resolution

FIG. 6.

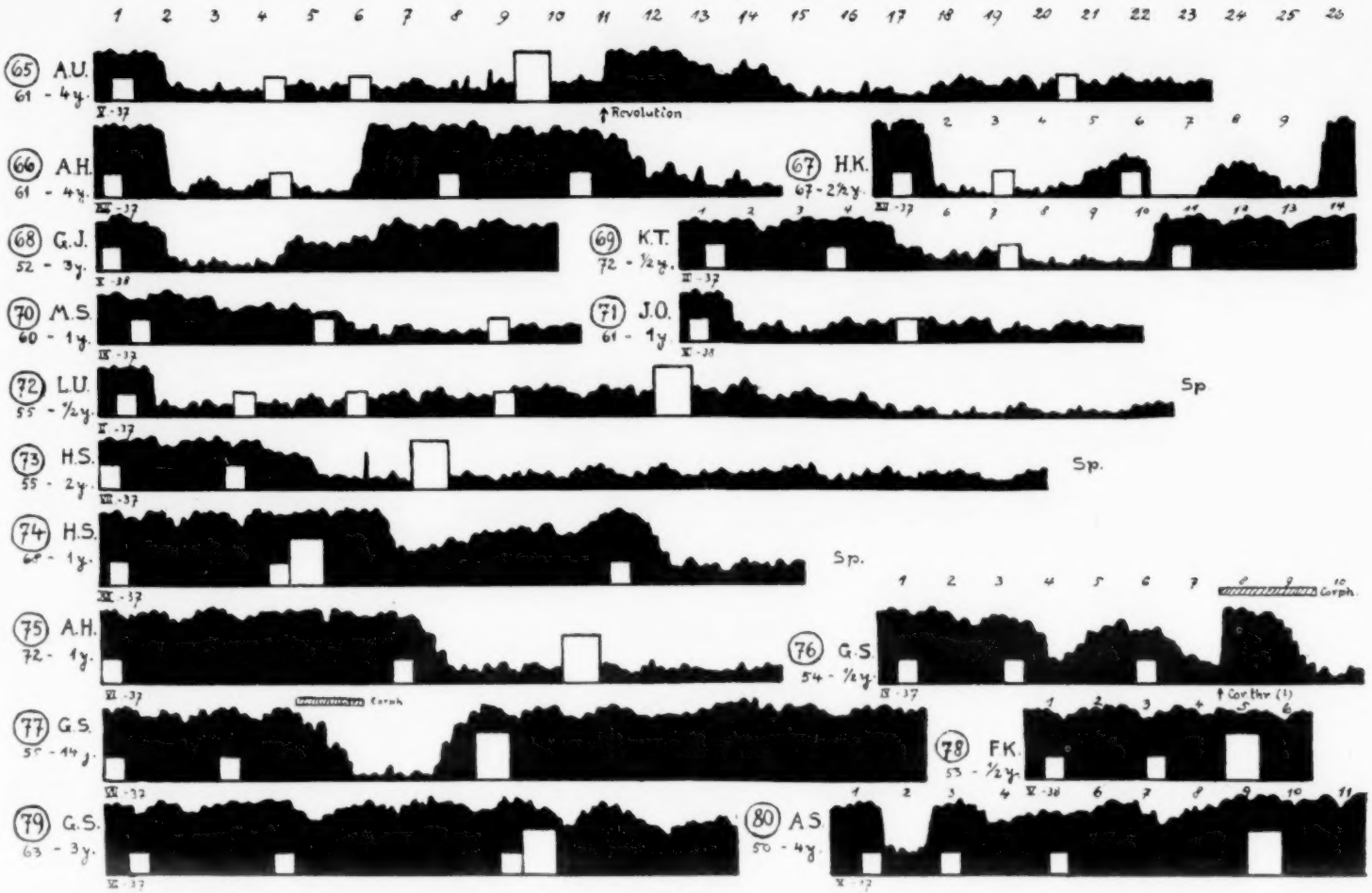
65 A.U. 61 - 4y.
66 A.H. 61 - 4y.
67 H.K. 67 - 2½y.
68 G.J. 52 - 3y.
69 K.T. 72 - ½y.
70 M.S. 60 - 1y.
71 J.O. 61 - 1y
72 L.U. 55 - ½y.
73 H.S. 55 - 2y.
74 H.S. 6? - 1y.
75 A.H. 72 - 1y.
76 G.S. 54 - ½y.
77 G.S. 5? - 14y.
78 F.K. 53 - ½y.
79 G.S. 63 - 3y.
80 A.S. 50 - 4y.
Revolution
Sp
Sp.
Sp.
Corph.
Corpus (1)

Fig. 7.

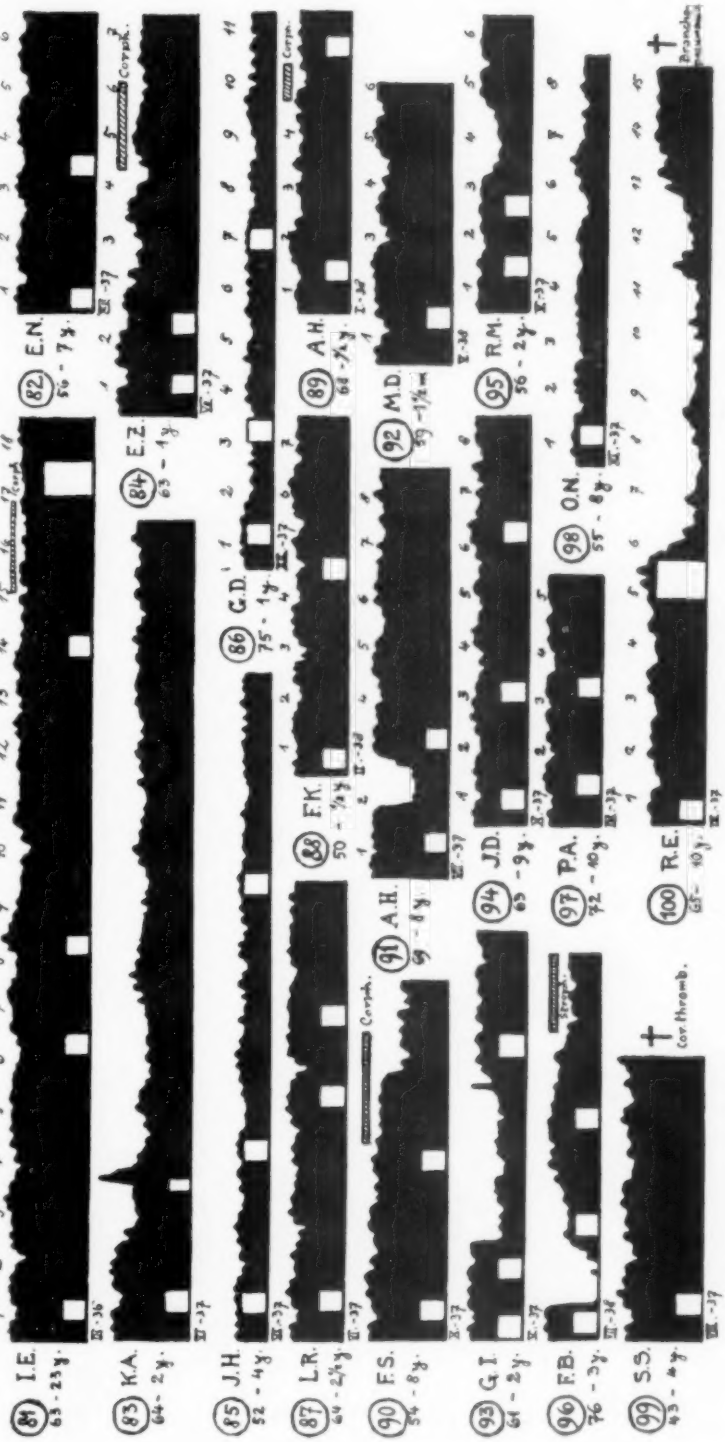
81 I.E. 63 - 23 y.
82 E.N. 56 - 7 y.
83 K.A. 64 - 2 y.
84 E.Z. 63 - 4 y.
85 J.H. 52 - 4 y.
86 C.D. 75 - 1 y.
87 L.R. 64 - 2½ y.
88 F.K. 50 - ½ y.
89 A.H. 64 - ¾ y.
90 F.S. 54 - 8 y.
91 A.H. 69 - 1 y.
92 M.D. 59 - 1¾ -
93 G.I. 61 - 2 y.
94 J.D. 63 - 9 y.
95 R.M. 56 - 2 y.
96 F.B. 76 - 3 y.
97 P.A. 72 - 40 y.
98 O.N. 55 - 8 y.
99 S.S. 43 - 4 y.
100 R.E. 65 - 40 y.
Cor thromb.
Bronchopneumonia

Fig. 8.

Fig. 7.

admission as a field laborer in a country into which he wants to immigrate. Patient 8 writes that in spite of the "terrible excitement" which she had to go through before leaving her native land, there was no relapse and that "a short time after the treatment the pressure near the heart as well as the pain in the left arm seemed to be blown away." An opera singer (number 13) writes "I have sung 85 great operas in this season without the slightest effort while before the irradiations I had very often more or less severe pain in the heart region." Four patients (2, 3, 34, 36) had resumed their habitual sport of mountain climbing, one of them (number 36) up to a height of 7000 feet. In this latter case the difficulty in walking had been so great before the treatment that the patient's daily walk from his home to his office, which was two-thirds of a mile, used to take him about 45 minutes. Patient 18 who was 41 years of age was able to take up strenuous physical training in a voluntary military formation after his long lasting anginal symptoms had disappeared. In 42 of the letters the writers ascribe the improvement of their condition expressly to the roentgen treatment. Many of them emphasize the complete or almost complete disappearance of their complaints, they report that they are again able to walk fast and to climb stairs, that they are no longer bothered by cold weather and that they have been able to reduce or to entirely omit the use of nitroglycerin.

A confirmation of the therapeutic efficiency of roentgen irradiation of the suprarenals in angina pectoris has been reported by Hadorn (Berne). In a recent personal letter he refers to a "sometimes amazing" improvement of the clinical state in about two-thirds of 25 irradiated patients and to several instances of normalization of the electrocardiogram after irradiation. Redisch (New York) has followed 11 cases of angina pectoris over one-half to one year after irradiation of the suprarenals. Seven of them (about two-thirds) were greatly improved insofar as the attacks disappeared almost entirely, two were moderately improved and two did not respond to the treatment. One of the latter died. Among the improved patients three series had been given in three cases, two series in three cases and one series in one case. Five of them were hypertensives. The blood pressure was not noticeably lowered.

Further personal communications in regard to good results from roentgen irradiations of the suprarenals in angina pectoris have been obtained from Prof. Schittenhelm (head of the Medical Clinic of the University of Munich) * who reported several cases of striking improvement without a relapse, lasting for two years, and from several practicing physicians of Vienna. Hutton [55] (Chicago) mentions the disappearance of precordial distress in five cases of arterial hypertension after combined irradiation of the pituitary and the suprarenal glands. Only von Zimmermann-Meinzingen [56] (Vienna) claims in a short note that the roentgen irradiation of the suprarenals is ineffective except for a "transitory psychogenic effect" and rejects it for undisclosed reasons.

* Received in September 1940.

A certain participation of psychogenic factors in the improvement of some of the cases is possible, of course, but it is certainly not decisive. This becomes evident from the fact that the subjective improvement does not take place earlier than several days or weeks after the irradiations, as a rule. Two or three series are not infrequently needed to produce a noticeable effect and in many patients other "impressive" treatments (injections, operations etc.) had been tried before without success. Finally the often very long-lasting absence of complaints after the irradiations, even in very severe cases, speaks clearly enough against a merely psychogenic effect.

Normalization of the Electrocardiogram

In 38 cases the electrocardiogram was examined before and after treatment. In 10 out of 13 improved patients who had shown signs of myocardial anoxia (depression of S–T flattening or inversion of T-wave) the electrocardiogram was found partly or completely normalized after roentgen-irradiation of the suprarenals (figures 9 to 14). This never occurred in patients whose complaints were not improved. Analogous findings were recorded by Hadorn,[25] according to a personal communication. Further comments on these observations have been published in Archiv für Kreislaufforschung by Raab and Schönbrunner.[48]

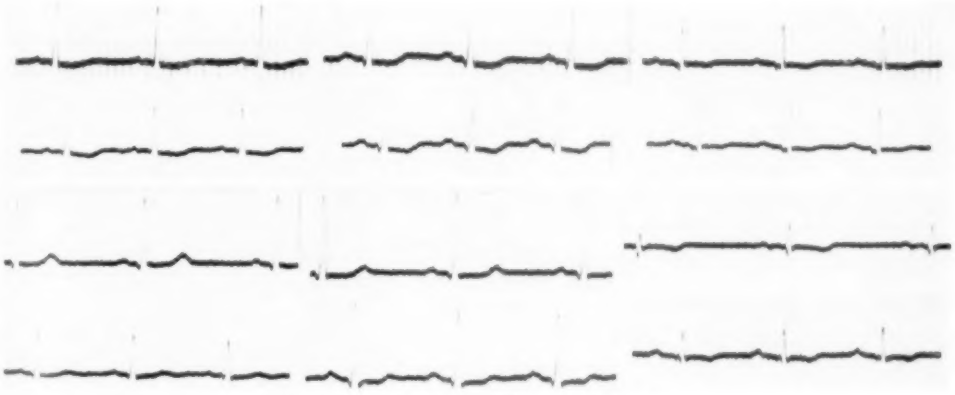

Fig. 9. Case 22, G. W., 69 years, ♂.
Above: Electrocardiogram at rest and after exercise before first treatment.
Below: Two months after first series of irradiation (for one month free of complaints).

Number of Series of Irradiations

In 21 cases one single series proved to be more or less sufficiently effective. Among the other 55 patients who were improved to various degrees, two series had been given in 22 cases, three series in 26 cases, and four series in 7 cases. The entirely unsuccessful treatments in 24 cases amounted to from one to four series with an average of two. It is possible,

of course, that the number of failures in the latter group could have been reduced by a further extension of the treatment. This is made obvious by the example of other cases in which the first series seemed almost or wholly ineffective while a second or third series was successful (for instance, cases 3, 8, 18, 25, 30, 32, 33, 37, 44).

Intervals of two to four months between single series seemed to be appropriate to provide for an optimal increase in efficiency.

Onset of Improvement after Irradiation of the Suprarenals

The onset of improvement took place at intervals varying from a few days to two months after the decisive series of irradiations; in most in-

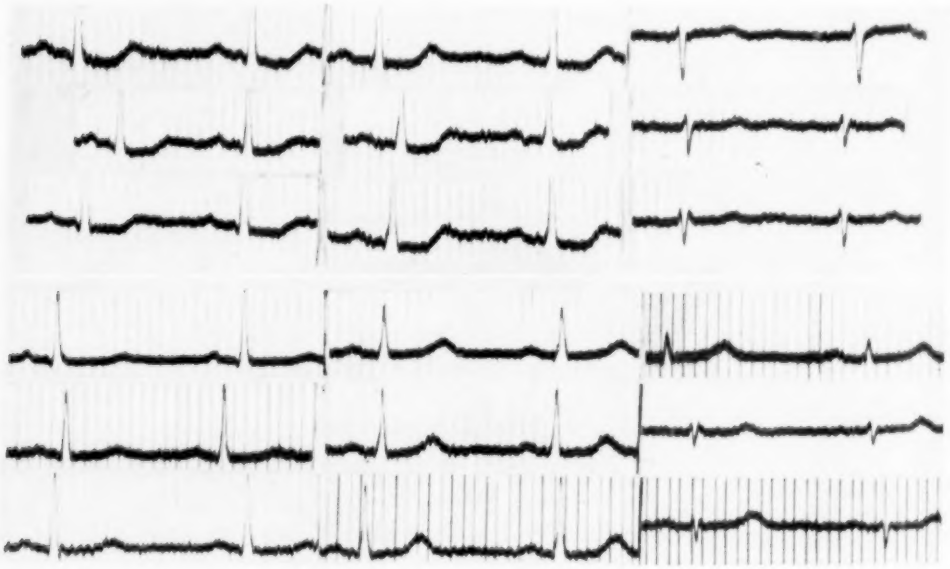

Fig. 10. Case 8, M. H., 65 years, ♀.

Above: Electrocardiogram at rest and after exercise before first treatment.
Below: Six months after second series of irradiation (for four months completely free of complaints).

stances, however, it was observed between the second and fourth week. This corresponds with the experimental findings in animals, whose suprarenal glands showed beginning histological changes in from a few days up to six weeks after irradiation (Cottenot[42]).

Relapses

Relapses of various degree and duration occurred in 20 among 76 improved patients. Some of them were only slight and disappeared soon by themselves (numbers 3, 32, 37, 43, 44), other ones could be stopped or at

least improved through renewed irradiations (numbers 10, 11, 28, 29, 30, 36, 40, 41, 43, 47, 52, 63, 66, 67, 74). In a few instances the relapse was not essentially influenced by further treatment of the suprarenals (numbers 60, 61, 69) or the treatment was discontinued (numbers 26, 55, 57, 58, 62, 68, 77).

Special attention has been paid to the effect of excitement and fear upon those 23 patients who belonged to the Jewish race and who had been improved through roentgen treatment. Only six of them (numbers 43, 44, 59, 62, 67, 77) suffered from a sudden relapse of their complaints immediately following the introduction of antisemitic laws into Austria after the reunion of that country with the German Reich (March 1938). In November 1938 when severe reprisals were taken for the assassination of a German diplomat by a Jewish youth, 16 of the aforementioned 23 Jewish patients were still under observation. None of them developed a relapse at

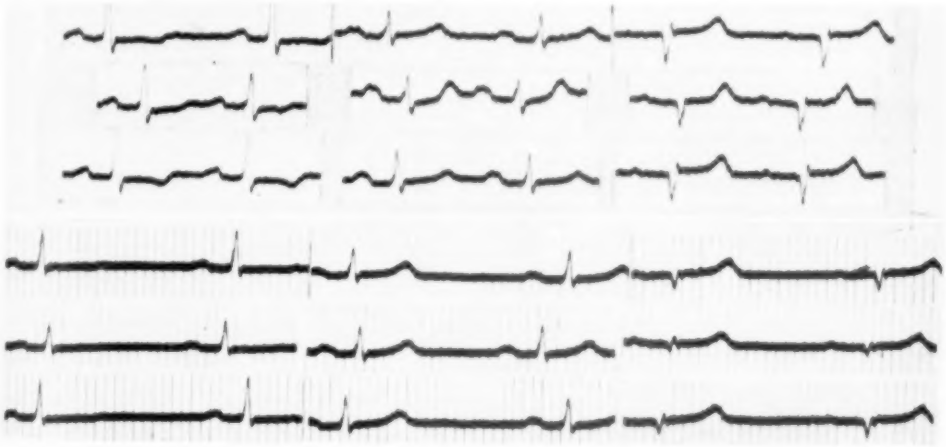

FIG. 11. Case 10, A. K., 43 years, ♂.

Above: Electrocardiogram at rest and after exercise before first treatment.
Below: Two and a half months after second series of irradiations (for two months almost free of complaints).
Seven and a half months after third series, during which time the complaints had disappeared completely, the electrocardiogram was found unchanged.

this time. In one case (number 55) a relapse occurred after the patient had lost his job.

BY-SYMPTOMS OF THE IRRADIATIONS

In no instance were there any signs of a *pathological* reduction of suprarenal activity such as general weakness, arterial hypotension, general hyperpigmentation, etc. No alterations of the irradiated skin occurred except for a slight brownish local discoloration in some instances. In several cases (numbers 3, 30, 43, 44, 50, 55, 56, 58, 63, 83) there was a slight or marked increase of stenocardiac complaints during or immediately follow-

ing the irradiations. It usually did not last but a few days, to be succeeded by partial or complete disappearance of the complaints. This phenomenon reminds one of the transitory reactions of the irradiated thyroid and of experimental findings concerning a transient hyperfunction of the suprarenal glands after irradiation. It has been observed chiefly in those few cases where attempts were made to give a larger dosage (300 r per session). Following these experiences the large doses were abandoned.

Nausea occurred in about 15 per cent of the cases during and immediately after the roentgen series but was distressing in only two or three instances in a total number of 224 series of treatments. More than 80 per cent of the patients did not complain of any discomfort whatsoever in connection with the treatment.

Behavior of Blood Pressure

The arterial blood pressure was 160 mm. Hg or more before treatment in 41 per cent of the cases. In none of them was a definite effect of the

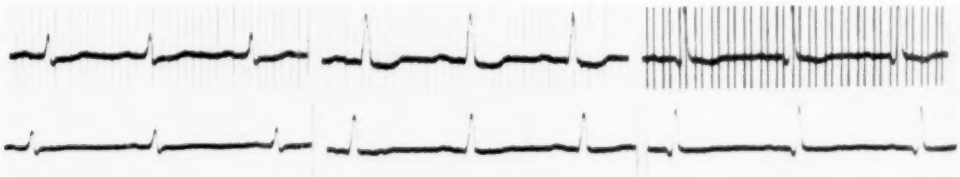

Fig. 12. Case 50, F. Z., 59 years, ♂.

Above: Electrocardiogram at rest before first treatment.
Below: Eight months after first series of irradiation (after seven months of considerable improvement, temporarily free of complaints).

irradiations upon the blood pressure observed. Some of the extremely hypertensive patients were more or less completely freed of their stenocardiac complaints without any lowering of the systolic pressure (for instance numbers 2, 8, 16, 32, 37, 49). In fact the blood pressure was often somewhat increased after the treatment (table 1). This is further confirmation of

Table I

Degree of Improvement after Irradiat.	Number of Cases	Degree of Complaints			Average Duration of Complaints (years)	Average Number of Series of Irradiations	Average Duration of Improvement (months)	Number of Relapses		Systolic Blood pr. (mm. Hg)		Average age (years)	Number of Deaths
		Severe	Medium	Slight				Total	Improved by Irradiations	Before Treatment	After Treatment		
+++ and ++	62	24%	58%	18%	3½	2	13½	20	12	155	158	60	1
+	14	43%	57%	0%	1¾	3	7½	9	3	151	161	61	0
−	24	50%	33%	17%	5⅓	2	—	—	—	172	180	60	2

the fact pointed out in another publication (Raab[57]) that the symptoms of angina pectoris are not essentially dependent upon the degree of mechanical strain put on the heart muscle through peripheral hemodynamic resistance. The average height of blood pressure before treatment in the group which did not respond to the irradiations was slightly higher than that in the groups which showed improvement (172 mm. Hg vs. 155 and 151 mm. Hg). Redisch's cases also did not show any change of blood pressure after irradiation whereas a lowering of blood pressure in essential hypertension can be produced through combined irradiation of the suprarenals and the pituitary gland according to Hutton.[55]

Occurrence of Coronary Thrombosis and Death

Seven patients had had thrombosis of the coronary arteries, according to their history, some time before the beginning of the irradiations. Six of these patients responded well to the treatment. The electrocardiogram which was taken in two of them after treatment was found partly normalized.

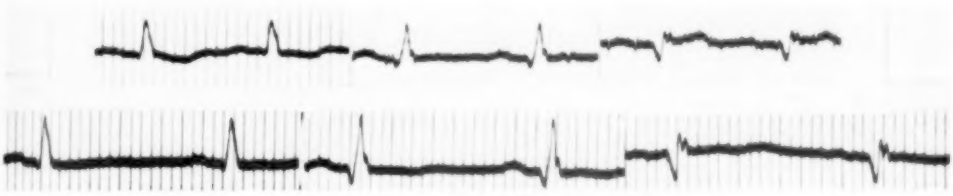

Fig. 13. Case 17, H. M., 72 years, ♂.

Above: Electrocardiogram at rest before first treatment.
Below: Three months after first series of irradiation (for two months free of complaints).

In three cases (numbers 31, 49, 99) a coronary thrombosis occurred several months after the irradiations, in two of them with fatal result.

Death occurred in the aforementioned case number 99 (4½ months after the first series) from coronary occlusion and in case number 100 from bronchopneumonia (14 months after the first series). In both of them the irradiation of the suprarenals had been ineffective. Patient number 49 seemed to be greatly improved at first—although his electrocardiogram remained unchanged—but he died from an attack of coronary occlusion four months after the irradiations. Besides these three deaths there were three other fatalities not included in the statistics of this paper because they occurred too early (one week, 8 days and 18 days) after the first series of irradiations. All of these patients died apparently from coronary occlusion. In one of them a fresh thrombus was found at necropsy. Whether or not these latter events had any causal connection with the foregoing irradiations cannot be decided. It should be emphasized, however, that sudden death is a common feature in angina pectoris and that one patient died and another

developed coronary occlusion, both within three days *before* the date fixed for the first irradiation. It is not possible, therefore, to draw any conclusion in either sense concerning an influence by irradiation of the suprarenals upon the tendency toward coronary thrombosis and death.

Contraindications

Contraindications for irradiation of the suprarenals have to be deducted from theoretical assumptions rather than from actual unfavorable experiences. The following may be mentioned: (1) Any symptoms of primary insufficiency of the suprarenal glands, (2) A coronary thrombosis within the past three months, (3) Tuberculosis of the kidneys or of the peritoneum, (4) Cardiac decompensation (insofar as no long-lasting improvement was seen in five severely decompensated patients with attacks of pulmonary

Fig. 14. Case 41, F. H., 63 years, ♂.

Above: Electrocardiogram at rest and after exercise before first treatment.
Below: One and a half months after the first series of irradiation (after five weeks of improvement).
Four months after the second series of irradiation, during which time the complaints had disappeared completely, the electrocardiogram was found unchanged.

edema, in spite of a few weeks' relief from pain in three of them). These cases are not included in the statistics of this paper.

Reasons for Failure of Roentgen Treatment

A definite explanation for the complete failure of roentgen therapy in about one-quarter of all cases cannot be given. As table 1 shows, there were no differences in the average age of these patients and those in the other groups. The average blood pressure was only slightly higher in the non-reacting group. The average duration of the disease was longer than in the well responding patients and also the degree of the complaints was somewhat higher in the majority of non-responding patients. These two

latter points may be of a certain importance but, nevertheless, there were also cases of the severest kind and of long duration among those who were almost entirely relieved of their complaints after the treatment (for instance numbers 1, 3, 20, 28, 31, 43).

The fact that stimulation of the sympathetic fibers of the heart produces the same reactions as adrenalin (specific increase of oxygen consumption with dilatation of the coronary arteries; Gollwitzer-Meier and Krüger [58]) suggests the possibility of a primary hyperirritability of the thoracic sympathetic nerves in certain cases which cannot be directly influenced by irradiation of the suprarenals but obtain benefit by irradiations of the chest (numbers 33, 48, 58, 100). Also the formation of adrenalin by the sympathetic neurones within the heart muscle itself (Cannon and Lissák [60]) may be of importance in these cases.

Individual Evaluation of Therapeutic Efficacy

As one or even two series of irradiations prove insufficient in some cases to give considerable and lasting relief, a patient must not be considered as definitely resistant to this therapy before three series have been applied at intervals of six to eight weeks and before a total observation period of five to six months has elapsed.

Furthermore attempts with other treatments must be avoided during this time, except for the use of nitroglycerin, if it is intended to draw clear conclusions.

Summary and Conclusions

1. *Theory:* Attacks of stenocardiac pain on effort, psychic emotion, cold, etc., are caused by anoxia of the heart muscle. This is largely due to acute discharges of adrenalin from the suprarenal glands occurring physiologically under the conditions mentioned.* Adrenalin exerts a specific anoxiating effect upon the heart muscle which is under normal circumstances compensated by simultaneous dilatation of the coronary arteries. This compensatory mechanism must fail when the coronary arteries are unable to dilate adequately due to coronary sclerosis and thus an abnormally exaggerated painful degree of myocardial asphyxia will result.

2. *Therapy:* Attempts to relieve the symptoms of angina pectoris by restricting the acute discharges of adrenalin through roentgen irradiation of the suprarenal glands were successful in 76 out of 100 patients. These patients had typical attacks of angina pectoris on effort, etc.; several cases were of the severest kind. Sixty-two patients were entirely or almost entirely freed from complaints or, at least, considerably improved for an average

* During the past year (1939–40) the correctness of this theory could be further evidenced through chemical determination of suprarenal hormonal compounds in the blood of normal individuals and of patients with angina pectoris at rest and after physical exercise, before and after roentgen treatment of the adrenal glands, and in the heart muscle of rats under similar experimental conditions. The results of these investigations are to be published at a later date.

duration of 13½ months. Fourteen patients were moderately improved during an average of 7½ months and 24 did not respond at all.*

Electrocardiographic signs of myocardial anoxia disappeared partly or completely in most of the successfully treated patients, but remained unchanged in those whose complaints were not improved.

The blood pressure, either high or normal, remained practically unchanged in all instances.

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In recent time 12 patients have been treated in Burlington by Dr. A. B. Soule. Two of them have not yet responded, 10 were completely or partly freed of their attacks for an average duration of 5 months up to date; nine of these 10 patients had received only one series.

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SPECIALIZATION IN INTERNAL MEDICINE*

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Examination of the roster of our College reveals that most of us are practitioners of internal medicine, indicating that we are primarily interested in the diagnosis and treatment of all medical diseases. Merely by being Fellows in this College, we not only avow such interest, but assert our ability to solve diagnostic problems and to undertake the treatment of patients. Of course, as the pathologist so often attests, all of us are diagnostically vulnerable, and therefore cannot claim infallibility; but in the main, most of you will, I think, agree with this description of our membership.

Let us break down the figures that appear in the 1939 Directory, so that we may learn just how you have designated yourselves in the realm of internal medicine. Among approximately 3000 Fellows, 899 of you state simply that you are practitioners or teachers of internal medicine; 1183 of you apparently practice internal medicine, and in addition a medical specialty, such as cardiology, allergy, gastroenterology, psychiatry and the like; 323 of you are not in active clinical practice, being radiologists, pathologists, officers in the Public Health Service, the Army or the Navy; 100 of you have retired; and approximately 484 of you (or 16 per cent) state that you practice a medical specialty solely. It is quite possible that this last figure is not entirely accurate, and might prove to be lower if we could get a personal report from each man who placed himself in a sub-specialty without including the whole field. However, those are the figures, and they must be accepted. And in a way, they are rather comforting. By that I mean that it is reassuring to find that only 16 per cent of our Fellows find themselves exclusively in the narrower fields of medical practice. Without considerable study it would be impossible to determine just how many of these 484 men have withdrawn from the large field in order to concentrate, and how many have started from scratch, so to speak, as medical specialists. It is to be hoped, at any rate, that the larger proportion of them fall into the first category, namely that of well-trained and experienced internists who have found their forte as consultants and teachers in the sub-specialties.

At this point a word about the place of sub-specialization in medicine would seem to be in order. None of us can doubt the high value of such endeavor among medical men. The extraordinary advance in our profession during the last 25 years has rested in no small measure upon the accomplishments of well-trained internists in the special fields of cardiology, gastroenterology, endocrinology, allergy, hematology, neurology, the control of infectious disease, and others. These men have refined diagnostic procedures, established standards of treatment, and given impetus to scientific

* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.

research in all branches of medicine. As consultants and teachers they have broadened the outlook of medical students, interns, and the profession at large. By their efforts, methods and implements of precision making for speedier and more accurate diagnosis have been developed and extended freely to the larger group of practitioners. They have stimulated the exhibition of specific treatment in various conditions, particularly those of an allergic nature, physiologic disorders, bacterial and virus infections, and functional disabilities of previously obscure etiology. Failing this group of so-called sub-specialists, we should indeed be years behind our present stage of accomplishment, and far below our present level of quality.

It may be of interest and should be of value to us all to consider the present status of sub-specialization in relation to a number of groups, including that of the specialists themselves, the rest of the profession (particularly internists), and the community at large. A number of questions at once present themselves. For example: How many sub-specialists should there be in proportion to all practicing internists, and what should be their relation to the rank and file of physicians? How should they be trained and developed? What should be their relation to the public?

The answer to the question of size must depend upon the nature of the sub-specialists' activity. That is to say, are they to serve merely as consultants and teachers, or should they make themselves directly available to the public? If they are to serve the profession primarily, then obviously there should be only a relatively few seasoned, high-grade consultants, whose primary function is to instruct and consult with physicians, to teach medical students and interns, and to further investigative work in their individual fields. If, on the other hand, the sub-specialists permit themselves to accept and treat patients directly, they must swell their number.

The problem of number brings up the next question, that of the training and development of young men in the special fields. How wise is it for a man after completing internship or residency to leap at once into allergy, gastroenterology, cardiology, and so forth, to the exclusion of general medical practice? Certainly if the apparent demand on the part of the public for such services increases, it will become almost obligatory for him to do so. Perhaps some of you believe that the best type of consultant in the sub-specialties has emerged from the ranks of internal medicine after some years of exposure to various types of cases, *in addition* to emphasis on one particular group. No doubt some of you think otherwise. In any case, we can give our attention to the whole subject without prejudice, and perhaps with some benefit to internal medicine in the future. Certainly no one can answer these questions categorically; but before an audience like this, composed largely of men representing internal medicine as practicing internists, among whom presumably there are less than 16 per cent representing the sub-specialties solely, the problem at least merits discussion, and it would seem relatively safe for me to express a few personal opinions on the subject.

Not long ago in a large teaching hospital a colleague of mine—a well-

trained internist—was asked by a fourth-year student: "In your own private practice do you treat cases of coronary thrombosis?" More recently a young medical intern inquired of another medical friend: "Do you treat lobar pneumonia in your private practice?" Now, both of these questions were put in good faith by serious-minded young men just entering the profession, and reflected, it seems to me, an attitude to be deplored. The mystery shrouding cardiology and the study of diseases of the chest seemed to them at the moment impenetrable. Such an attitude makes one wonder just what is the trend in the education of internists. The trouble apparently starts early in a young man's medical training today, certainly during the fourth year, perhaps even earlier. He sees a patient admitted to the ward for diagnostic study and assigned to him. Not infrequently before he has had time to obtain an adequate history, examine the patient, or give his difficulty thoughtful consideration, occasionally even before the case has been properly reviewed by the men in charge, there appear on the record one or more expert opinions by various consultants. Often under such conditions the diagnosis is quickly made and treatment is advised. What results? The student is apt to accept the verdict as final, say to himself "Well, that's that," and pass on to other duties. The only person who has advanced himself intellectually is the consultant. The younger man does not know quite how the thing has been done, but is willing to believe in the result, still retaining his mystification as regards the expert. In such an atmosphere, one can well understand how the men quoted above came to put their questions to my confrères.

Please do not misunderstand me. Such a situation is by no means the rule in our teaching centers; but this hypothetical episode does serve to illustrate a distinct tendency in contemporary medical education, a tendency that some of us believe must be combated.

Our young graduate, after finishing his internship and perhaps his residency, now has to consider his future. Shall he face the troublesome complexities of general internal medicine, or shall he attempt to tear away that cloud of mystery surrounding some specialty and become at once an expert himself? There is nothing, of course, to prevent his learning a medical specialty while he continues his work in medicine, but often the narrower path appears much smoother, and, incidentally, the financial returns quicker and larger. The latter aspect, that of earning a comfortable livelihood, is again modified at once by the number of men joining him in sub-specialization. If the public demand for his specialty becomes quickly filled—following the law of supply and demand—he must then resort to the practice of general internal medicine, certain features of which he may have neglected; and because of such neglect there is always the possibility that he will practice it to the detriment of the public.

We know that the competent, seasoned specialist-consultant prefers *not* to be consulted directly by patients; but if young students and interns (who are to become practitioners) have acquired the habit of turning at once to

an expert in a sub-specialty, how can we expect the man on the street to do other than to reflect their attitude by going directly to the office of a psychiatrist, a gastroenterologist, an expert in hypertension, in asthma, or even in dreams?

In this connection let us recall what was said by C. M. Jones,[1] past president of the American Gastroenterological Association, in his presidential address in 1937. After tracing the development of knowledge about the gastrointestinal tract, and mentioning certain men responsible for such progress (Beaumont, Pavlov, Roentgen, Cannon, Castle, Dale, Gamble, Ewald, Cushing and Banting among others), he continued:

"In spite of the many obvious omissions and deficiencies in the above list of men, it is clear that progress in gastroenterology, whether that term be taken to mean the science, the clinical understanding, or the therapeutics of digestive diseases, has never emanated from a group of men whose sole interest was necessarily directed toward a study of the gastrointestinal tract. Practically none of the men whose names are mentioned above could by the broadest stretch of imagination be classed as gastroenterologists. In other words, it is most essential that the members of a gastroenterological association be interested in and capable of discussing a multiplicity of apparently unrelated medical subjects, and that a practicing gastroenterologist must be equally catholic in his information, interests and training, if he is to give adequate and intelligent service to his patients. I am becoming more and more convinced that the scope of an association such as this must be kept a wide one, and that emphasis must be constantly placed, not on the narrow concept implied in the term gastroenterology, but upon a much broader and better balanced conception of the subject and its practice. *The only real danger lies in attempting to narrow the field*, and to my mind any attempt to emphasize the specialty rather than the special interest spells a lowering of values and a diminution in the quality of medical service."

For me to suggest how specialists in medicine should be trained would indeed be presumptuous, even if it were entirely pertinent to the question at hand, but let me quote a few sentences spoken by Dean Burwell[2] of the Harvard Medical School at your last year's meeting in New Orleans, when discussing postgraduate medical education.

"Not only may special groups become concerned with parts of people and lose touch with the wider problem of the whole patient," he said, "but such groups may actually become isolated and lose some essential contact with other fields. This may not be very serious for the first generation of specialists in a given field, but it might be really grave for their students or their students' students. This suggests to me the daring hypothesis that perhaps no group should be wholly responsible for the training of its own successors. Is it not one of the advantages of bi-sexual reproduction that sons do not in all respects resemble their fathers?"

Now if, as I fondly hope, some of you agree with me that a tendency

toward too early and too frequent specialization exists in the ranks of internal medicine, and that such a tendency deserves some restraint—if you believe, in other words, that we should make an attempt to put our house in order in that regard, then what are you willing and able to do about it? There is much that *can* be done.

First of all, those of you who are teachers in medical schools and hospitals can accomplish much through your personal influence upon students, even during their earlier years. Let them understand the value of independent approach to all medical problems; inspire in them the ambition to "see through" for themselves, and to voice their opinions before calling upon the experts. Teach them the value of consultation and how to make intelligent use of consultants. Convince them that the exercise of their own intellectual equipment is of far greater importance than being right—that being wrong is not of itself a cardinal sin. Show them that the man who is always "right," the man who knows all the answers, is more often wrong than right. As the students grow older, advancing to the practice of their profession, urge upon them some special interest, demanding that they keep themselves the while exposed to all types of cases, both in the clinic and, as may happen, in private practice. Demonstrate to them the fallacy of attaching themselves exclusively to any instrument of precision, pointing out to them the spectacle of the well-known tail wagging the dog!

Further, what can you specialists do for these young men? Among other things, you can put freely at their disposal all the details of your specialty, encourage their interest in your special field, inspire them to take up investigative studies, show them the interrelation between your limited field and the other branches of medicine—and, in the process of so doing, learn much from them yourselves. Yours is a high responsibility, because without you the quality of medical practice would suffer much. But if you go hand in hand with the great body of internists, directing your efforts properly, the future progress of internal medicine remains secure.

Lastly, what can all of us as internists-at-large, that is to say, as physicians, do to attain the desired objective? To begin with, we can back up whole-heartedly the bona fide, well-trained and seasoned specialists. We can see to it that their path is made easy for self-training and for the teaching of selected younger men. We can use them as consultants to the advantage of ourselves, our patients, and incidentally to themselves. We can discourage their segregation, particularly by welcoming them into our larger groups and societies, and by opposing the formation of numerous minor groups. Above all, we must prevent as far as possible the establishment of minor qualifying boards. In any event, the National Board of Internal Medicine should be the fundamental qualifying body, the starting point, at least, from which men may, if it seems necessary, go on to further qualification by boards of narrower scope. But is it possible that the day will come when a man will be qualified to engage in the treatment

of hypertension, of asthma, of tachycardia, of nocturia, of heartburn, or even insomnia? God save the mark!

Fortunately, internal medicine is still in a reasonably healthful condition, and no doubt will remain so. Moreover, we can all give it a hopeful prognosis, knowing as we do how deeply planted are its roots. The parent body is growing steadily in numbers and in strength. It will undoubtedly survive this minor malady. The very fact that we are aware of a trend which threatens to overreach itself demonstrates that the cure or correction is already half accomplished.

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CASE REPORTS

ABERRANT PANCREAS, WITH REVIEW OF THE LITERATURE AND REPORT OF A CASE*

By Daniel B. Faust, M.D., F.A.C.P., and Charles S. Mudgett, M.D., F.A.C.P., *Washington, D. C.*

Klob first reported the aberrant pancreas in 1859. Since then pancreatic tissue has been frequently found in various organs of the abdominal cavity. Defective embryological development is probably responsible for small masses of pancreatic cells being pulled off from the main organ in the developmental process. These small masses may be found in almost any part of the gastrointestinal tract and are located usually between the mucous and serous layers. The histology of aberrant pancreatic tissue is not different from that of the main organ.

There is also evidence in the literature that these aberrant masses are at times the site of or the origin of carcinoma. At operation the tissue is frequently mistaken for some type of tumor. Some of the aberrant pancreatic masses seem to have normally formed ducts that open into the lumen of the bowel. In other instances, gastrointestinal disturbances are caused by the mechanical effects due to the growth of the aberrant tissue. It is interesting to note the impressions of some of those who have reported cases in the past.

Montgomery,[1] as early as 1861, reported two cases. One was his own case, in which the tissue was located in the jejunum. He was not able to find any ducts in this one. The other case was one that had been written up in the autopsy book nine years previously by Dr. Bristowe, who identified pancreatic tissue located in the ileum.

In 1888, Van Gieson [2] reported two cases with pancreatic tissue situated in the duodenum. One was found in a newborn child causing obstruction of the bowel, and the other was in an adult male. Note was made by him at the time of the danger of mistaking such masses for carcinoma.

Thatcher [3] reported an accessory pancreas in 1893, and Biggs,[4] in the same year, reported a supernumerary pancreas in the pylorus of an alcoholic. He stated at the time that this anomaly would be found in nearly one-third of all necropsies, if careful search were made. It was also his opinion that ducts were found throughout such tissue, but not well marked, and that he could not say where the ducts emptied.

In 1900, Nicholls,[5] reported an aberrant pancreas in the duodenum discovered at autopsy in a young boy with tuberculosis of the lumbar vertebrae. Three years later, in 1903, Ruediger [6] reported an accessory pancreas and stated at the

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time that he was able to find only 20 authenticated cases. He reported ducts in the mass of pancreatic tissue, but was not certain that they opened into the lumen of the bowel. The mass was found in the jejunum. It was his impression that accessory pancreatic tissue located in such places might cause diverticuli, intussusception, or obstruction of the intestine.

One year later, in 1904, Turner [7] reported another case of aberrant pancreas, located in the jejunum, in a 15 year old female. He stated that the accessory pancreas in this instance contained ducts that opened into the bowel. He stated that such rests were not common and were significant because they might sometimes be the starting point of tumors in unusual locations. Also, in 1904, Warthin [8] reported two cases. In one, the pancreatic tissue was located in the greater omentum, and in the other, it was found in the anterior wall of the stomach.

Lewis,[9] in 1905, reported a case discovered at autopsy in which the aberrant tissue was located 85 cm. below the pyloric orifice, and noted that the ducts were apparently patulous. He stated that the condition was frequently found in lower animals, and not infrequently in man. He also advanced the idea that such aberrant masses of pancreatic tissue might prevent diabetes mellitus, as the accessory organ might escape the disease affecting the main organ in this disease.

Finkelstone,[10] in 1911, stated that this condition was not rare, and in the same year reported an aberrant pancreas in the wall of the intestine located 30 cm. from the pylorus. Gibson,[11] in 1912, reported an aberrant pancreas in the pyloric end of the stomach. The patient's gastrointestinal symptoms were so persistent and severe that the abdomen was explored. The mass of pancreatic tissue was removed from the wall of the stomach; however, the same symptoms returned later, and it was evident that the accessory pancreas had not caused them.

In 1913, Weidman [12] reported an aberrant pancreas located in the capsule of the spleen. Also, in 1913, Carwardine [13] reported an accessory pancreas in a girl 12 years of age. It was located in the jejunum. The symptoms were those of obstruction of the bowel. Exploration revealed the nodule to be in a state of acute necrosis with swelling of the bowel in this region, causing almost complete obstruction. Posterior gastrojejunostomy was performed, but the patient died. Autopsy was refused. He stated that an accessory pancreas might give trouble by one or more of four methods; viz., " (1) it may produce mechanical alterations in the walls of the alimentary canal; (2) the accessory pancreas is liable to acute pancreatitis; (3) accessory pancreas may complicate the diagnosis of the cause of abdominal complications; (4) accessory pancreas may develop chronic interstitial pancreatitis."

In 1916, Weidman [14] reported another case in which the pancreatic tissue was located in the duodenal wall. In this same year, Weidman [15] again reported a case, this time located in the wall of the jejunum.

An aberrant pancreas located in the duodenum was reported by Reimann [16] in 1918. The patient was 54 years old, a male who had diabetes mellitus and a duodenal ulcer. During this same year Benjamin [17] reported an accessory pancreas that caused intussusception in the upper part of the jejunum. The pathological diagnosis of the case was adenoma of aberrant pancreas.

In 1921, Cafritz [18] reported an interesting case in which because of epigastric pain, vomiting, and a long tender appendix retaining barium at 72 hours, he

explored the abdomen. No pathological process was found except a chronically inflamed appendix, and an aberrant pancreas located in the duodenum, which he removed. He concluded that the accessory pancreas did not cause symptoms in this case, but in similar cases should be removed provided the true pancreas was normal in appearance, size, and consistency.

In 1921, Horgan [19] reported two cases. One was located in the duodenum and the other in the posterior wall of the stomach, near the greater curvature. Also in 1921, Cohen [20] reported an aberrant pancreas located in the pylorus producing among other gastrointestinal symptoms that of partial obstruction. There was a gastric ulcer over the mass in the wall of the stomach. It was his belief that chemical irritation of adjacent tissues by pancreatic juice should be considered, and he thought this was the cause of the ulcer in his case. He also mentioned obstruction, ulcer, intussusception, diverticuli, and pancreatitis as the surgical complications that might be expected in aberrant pancreas.

Choisser,[21] in 1925, reported an aberrant pancreas located in the pylorus. The mass was discovered at operation and was thought to be a carcinoma. It was removed and later identified by pathological study as an accessory pancreas.

Weeks and Steinke,[22] in 1927, reported a case in an infant girl two months old. The accessory pancreas was located in the duodenum. Exploration and later autopsy studies revealed, in addition to the aberrant pancreas, congenital atresia of the bile ducts and biliary cirrhosis. Also in 1927, Simpson [23] reported a case in which the pancreatic tissue was located in the wall of the stomach and resembled a gastric ulcer.

Cave,[24] in 1928, reported a case in which the tissue was located in the duodenum. This case mimicked clinically a duodenal ulcer.

Moore [25] reported a case in 1929. The pancreatic mass was located in the jejunum in an infant one year old. The child died from laryngeal obstruction. He concluded with the opinion that the origin of these congenital anomalies was either by adhesions of the main anlage or from anomalous anlage, and that accessory pancreases were in rare instances the underlying cause of diverticuli and intussusception, and the site of the origin of carcinoma.

Also in 1929, Cox [26] reported an aberrant pancreas located in the pylorus near the pyloric ring, which apparently produced partial obstruction. Nausea, vomiting, epigastric pain, loss of appetite, sleeplessness, and loss of weight were the principal symptoms. He also reported a reduced amount of hydrochloric acid. Exploration revealed an aberrant pancreas located in the pylorus which was removed. A gastroenterostomy was performed, which apparently relieved the patient.

Farr,[27] in 1930, reported an aberrant pancreas located in the jejunum. There was also a duodenal ulcer with marked obstruction and gastric retention.

In 1931, Ross [28] reported a case very similar to one previously reported by Benjamin,[17] in which intestinal intussusception was caused by an aberrant pancreas. Ross described the mechanism of the production of the intussusception. The diagnosis was adenoma of aberrant pancreas, and Ross stated at the time that his was the second case recorded in medical literature of aberrant pancreas causing intussusception.

Bookman,[29] in 1932, reported an aberrant pancreas in the duodenum in which carcinoma developed. In the same year Crosby and Graham [30] reported a case

located in a dermoid cyst in the anterior mediastinum of the chest. Preoperative diagnosis was intrathoracic goiter. Removal was successful.

King and McCallum [31] reported four cases in 1934, and offered evidence that aberrant pancreatic tissue was not a "cell rest" and did not arise during embryonic life. They believed it arose from differentiated tissue usually developing in adult life. The reasons given for believing this were that such tissue was directly or indirectly connected with the overlying epithelium, and that in some cases direct continuity could be established between the pancreatic tissue and gastric epithelium. In addition, distribution of such tissue in the stomach corresponded to the usual locations of gastric ulcers. Furthermore, the tissue was usually found in adults and old people. Another reason was that there was no morphologic connection between these masses and the anatomic pancreas; and the final ground for the belief was that the aberrant masses were not discrete, but were intermingled in localized areas with normal structures of the wall of the stomach.

Best and Bowers,[32] in 1934, stated that the condition is a defect of embryological development and is a surgical condition not often producing symptoms. They further pointed out that when symptoms are produced they are usually interpreted as being due to cholecystitis, peptic ulcer, or malignancy.

In 1935, Hunt and Bonesteel [33] reported a case in which the aberrant tissue was located in Meckel's diverticulum and in which the symptoms resembled those of appendicitis. These authors reported the fourteenth case recorded in this location. They presented a summary of cases with location, up to 1932, as shown in table 1.

TABLE I

Distribution of Aberrant Pancreatic Tissue as Found by Hunt and Bonesteel

Location	Warthin 1904	Horgan 1921	Simpson 1927	Hunt and Bonesteel 1932	Total	%
Wall of stomach	14	8	25	12	59	31.7
Wall of duodenum	10	4	14	12	40	21.5
Wall of jejunum	13	13	10	3	39	20.9
Wall of ileum	1	1	2	0	4	2.1
Wall of intestine (not located)	1	1	1	0	3	1.6
Diverticulum of stomach	1	0	2	0	3	1.6
Diverticulum of duodenum	0	2	0	1	3	1.6
Diverticulum of ileum	2	3	4	4	13	7.0
Meckel's diverticulum	3	1	6	3	13	7.0
Umbilical fistula	1	0	0	0	1	0.5
Mesenteric fat	1	0	0	0	1	0.5
Omentum	1	0	0	0	1	0.5
Splenic capsule	0	1	2	0	3	1.6
Gall-bladder	0	0	1	1	2	1.1
Total cases	49	34	67	36	186	

In 1935, Branch and Gross [34] reported 24 cases collected from the records of the Boston Children's Hospital and the Peter Bent Brigham Hospital. Four of these cases produced pathological changes; viz., one causing pyloric obstruction, and the other three, ulceration of the stomach or duodenum.

Also in 1935, Poppi [35] reported a series of 300 cases, which is the most complete to date. These were collected from the literature since 1727. In some

instances, especially in the earlier reported cases, the diagnosis may be questionable. Table 2 gives the distribution in the various locations as found by Poppi in his review. In comparing this with the distribution as found by Hunt and Bonesteel,[33] as given in table 1, we note that these authors found, in addition

TABLE II

Distribution of Aberrant Pancreatic Tissue in the Cases Reviewed by Poppi in 1935

Stomach	80	Diverticulum (not located)	1
Duodenum	84	Umbilical fistula	1
Duodeno-jejunal angle	2	Mesentery	3
Jejunum	57	Omentum	4
Ileum	10	Splenic capsule	1
Small intestine (not located)	6	Spleen	1
Diverticulum of stomach	3	Gall-bladder	3
Diverticulum of duodenum	5	Cystic duct	1
Diverticulum of jejunum	1	Gastro-colic ligament	1
Diverticulum of ileum	8	Transverse mesocolon	1
Meckel's diverticulum	9	Location questionable	16
Diverticulum of small intestine (not located)	2	Total cases	300

TABLE III

Cases of Accessory Pancreas Recorded in the Literature Since Poppi's Review in 1935

Year	Author	Stomach	Diverticulum of duodenum	Duodenum	Meckel's Diverticulum	Jejunum	Ileum	?	Total
1932	Picena, J. P.[36] *					1			1
1933	Ayzenberg, A. A.[37] *	1							1
1933	Ross, K.[28] *						1†		1
1934	King, E. S. J. and McCallum, P.[31] *	4							4
1934	Ugelli, L.[38] *	1		2		2			5
1934	Best, R. R.[32] *			2					2
1934	Nishirvo, T.[39] *							1	1
1935	Branch, C. D. and Gross, R. E.[34] *	3	1	9	6	4	1		24
1935	Ciceri, C.[40] *			1					1
1935	Gilbert, R. and Bardet, P.[41] *	1							1
1935	Best, R. R.[42] *	1							1
1935	Azzolini, O.[43] *						1†		1
1936	Stohr, R. and Kogler, K.[44]			1					1
1936	Ugelli, L.[45]		1						1
1936	Nakamura, T.[46]					1			1
1936	Donovan, R. E. and Aguirre, A. C.[47]							1	1
1937	Whiteside, W. C.[48]			1					1
1937	Heilig, W.[49]			1					1
1937	Hill, F. C. and Cohen, L.[50]				1				1
1937	Fanta, E.[51]			1					1
1938	Danzis, Max[52]	1		1					2
1938	Zaslavskiy, L. D.[53]	1							1
1938	Mazzini, O. F.[54]			1					1
1938	Udaondo, C. B. and Jaca, J. A.[55]	1							1
1938	Branscheid, F.[56]			1					1
	Total cases	14	2	21	7	8	3	2	57

* Not included in previous articles, but recorded in the literature prior to 1935.
† Cases complicated by intussusception.

to those cases reported by Poppi, five cases in the ileum, five cases in Meckel's diverticulum, and two cases in the splenic capsule.

In reviewing the literature since 1932 a number of cases have been found which were not included by either Poppi [35] or by Hunt and Bonesteel [33] in their reports. These cases, with those found reported since 1935, are listed in table 3.

The distribution of aberrant pancreatic tissue in the gastrointestinal tract, as far as we have been able to determine from available reports, including the case reported in this paper, is given in table 4.

TABLE IV

Distribution of Aberrant Pancreatic Tissue with Percentage Incidence

	No. of cases	%		No. of cases	%
Stomach	95	25.67	Diverticulum (not located)	1	.27
Duodenum	105	28.37	Umbilical fistula	1	.27
Duodeno-jejunal angle	2	.54	Mesentery	3	.81
Jejunum	65	17.56	Omentum	4	1.08
Ileum	18	4.85	Splenic capsule	3	.81
Small intestine (not located)	6	1.62	Spleen	1	.27
Diverticulum of stomach	3	.81	Gall-bladder	3	.81
Diverticulum of duodenum	7	1.89	Cystic duct	1	.27
Diverticulum of jejunum	1	.27	Gastro-colic ligament	1	.27
Diverticulum of ileum	8	2.16	Transverse mesocolon	1	.27
Meckel's diverticulum	21	5.67	Location questionable	18	4.86
Diverticulum of small intestine (not located)	2	.54	Total Cases	370	

CASE REPORT

J. H. B., a white male, aged 43 years, was admitted to Walter Reed General Hospital, Washington, D. C., on April 12, 1938. His previous personal and family history is not important. He entered the hospital complaining of diarrhea, generalized abdominal pain, anorexia, and weakness. These symptoms were not related in any way to meals. They had been present for more than a year, and the patient had been hospitalized five months previously, at which time a careful study of the gastrointestinal tract had been made with negative findings. The general physical examination revealed obesity (weight 208 pounds), slightly enlarged thyroid, moderate generalized abdominal tenderness on deep palpation, chronic follicular tonsillitis, and edentulous maxillae. Laboratory and roentgen-ray examination revealed a polyp located in the pyloric end of the stomach (figure 1), an absence of free hydrochloric acid in the gastric juice, with only slight response after the administration of histamine, and a repeatedly low basal metabolic rate (minus 25 per cent to minus 47 per cent).

Because of the belief that the polyp was the cause of the gastrointestinal symptoms, resection was recommended. A subtotal gastrectomy was done, and the following pathological report was received: "Grossly: a cup-shaped section of the wall of the pylorus of the stomach, approximately 5 cm. in diameter. The base of the depression presented a teat-like elevation upon the mucosal surface. Microscopic: Three sections were studied. The mucosa was of ectopic intestinal type; the glands (Lieberkuhn) were long, and lined with cylindrical mucous cells. Some of the glands were cystic and included mucus, and polymorphonuclear leukocytes. The lymphoid tissue was hyperplastic. The muscularis mucosa was intact. The submucosa included (*a*) many glands of Brunner type; (*b*) quite a large compact fragment of pancreatic

tissue consisting of acini, but no island parenchyma; (*c*) quite large ducts lined with cylindrical cells with pale cytoplasm and normally placed nuclei, with dilatation of some of the ducts. The muscle wall was normal other than for slight diapedesis of polymorphonuclear leukocytes through the walls of arterioles and precapillaries. None of the epithelial elements showed evidence of malignant (atypical) change

FIG. 1. Roentgenogram of stomach showing filling defect at the pars pylorica, suggestive of a polyp, with a central fleck of barium in the ostium.

(figures 2 and 3). Pathological diagnosis: developmental anomalies (aberrant pancreatic tissue in submucosa; dilated ducts and ectopic intestinal type gastric mucosa); low grade chronic inflammatory reaction."

The patient made an excellent recovery from his operation and for a short time seemed to be free of all symptoms. This, however, did not last long; the same symptoms returned and have been present ever since. It is now evident that the accessory pancreas did not cause the gastrointestinal symptoms in this case.

SUMMARY

Aberrant pancreatic tissue may occur at any part of the gastrointestinal tract, and occasionally elsewhere. The most frequent sites are the duodenum, stom-

ach, and jejunum, in order. Meckel's diverticulum and the ilium are also fairly frequent sites. Defective embryological development is the most likely explanation of the occurrence of this anomaly. In the stomach, as in the case presented, the tissue frequently appears as a polypoid mass on roentgen-ray examination, and at other times it may appear as an ulcer. It is impossible, obviously, to diagnose pancreatic tissue in any location, except by microscopic examination of

FIG. 2. Photomicrograph of mass removed from stomach showing a cross section of the wall of the stomach and collections of pancreatic tissue in the submucosa. (Army Medical Museum, No. 67778, Acc. No. 60222.)

tissue removed at operation or at autopsy. When the tissue is located in the stomach, as in the case reported, its removal does not always relieve symptoms. In the stomach, as elsewhere, it may be the site of acute inflammation, perhaps with ulceration or necrosis; and, when located in the ileum, it may occasionally cause intussusception. If these changes are present surgical removal is indicated, and, if successful, will undoubtedly relieve the acute symptoms.

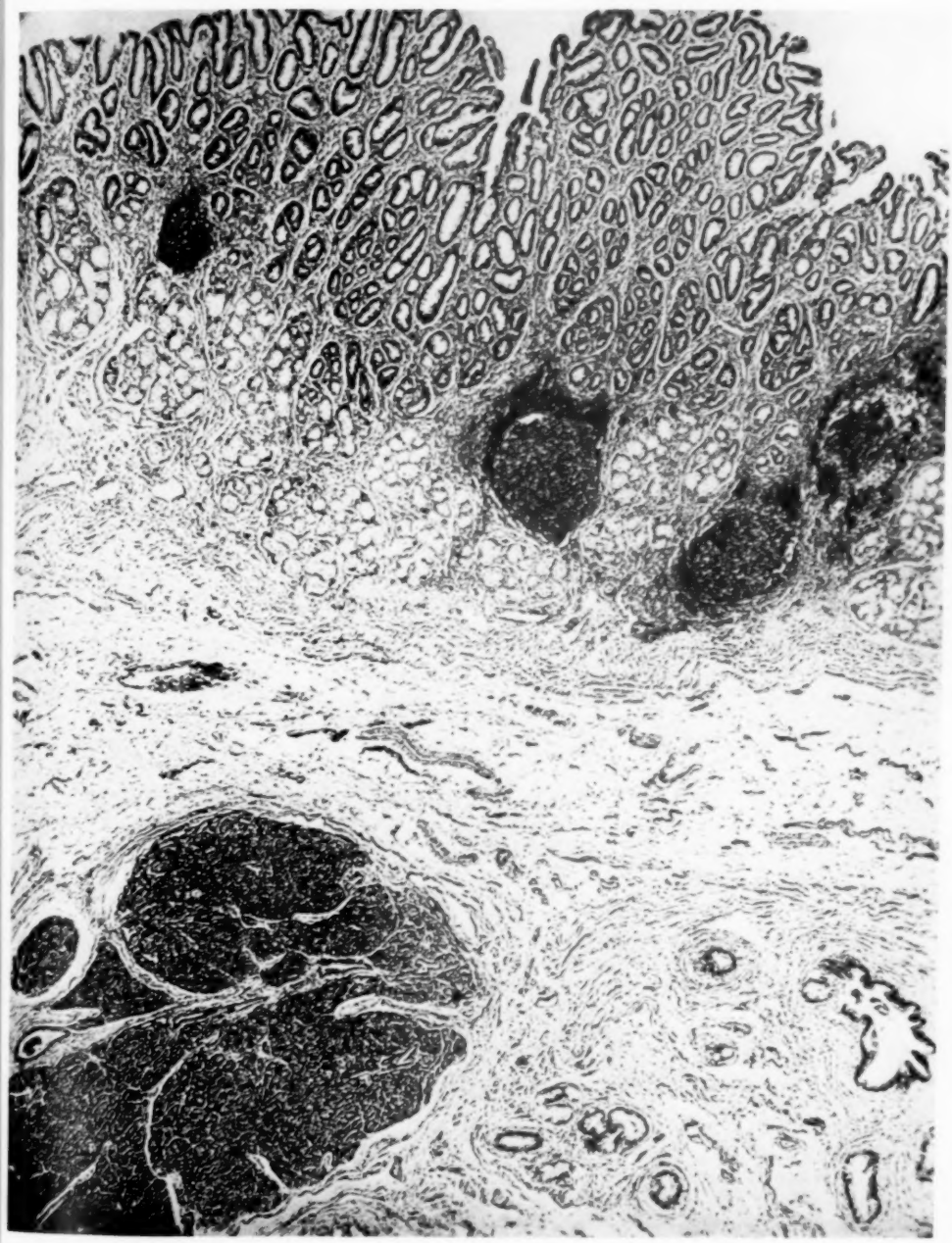

FIG. 3. Photomicrograph of mucosal and submucosal layers through mass, showing (*a*) intestinal type gastric mucosa, (*b*) masses of pancreatic acini in the submucosa, and (*c*) dilated ducts. (Army Medical Museum, No. 67778, Acc. No. 60222.)

Conclusions

1. The literature on aberrant pancreatic tissue is reviewed and 58 cases added to those previously summarized, bringing the total reported to date to 370.

2. The frequency of occurrence in the different parts of the gastrointestinal tract is stated.

3. A case of aberrant pancreatic tissue in the wall of the stomach, appearing as a polyp on roentgen-ray examination, and removed without relief of the gastrointestinal symptoms, is presented.

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TUMORS OF THE HEART. II. REPORT OF A SECONDARY TUMOR OF THE HEART INVOLVING THE PERICARDIUM AND THE BUNDLE OF HIS WITH REMISSION FOLLOWING DEEP ROENTGEN-RAY THERAPY *

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THE first paper of this series [1] included a description of the first reported case of a primary tumor of the heart recognized before death in a patient in whom there was no previous knowledge of tumor elsewhere in the body.† The diagnosis was simple and logical, the same reasoning being applied to a rapidly recurring sanguinous pericardial fluid that has been applied many times to a similar pleural effusion. In that report it was suggested that roentgen-ray therapy might have helped the patient had it been tried early. Curiously enough, as often happens in the practice of medicine, we soon had the privilege of observing a case of a metastatic tumor of the heart which responded promptly to roentgen-ray therapy, though metastases elsewhere resulted in death five months later.

There have been a number of cases of metastatic tumors of the heart which were diagnosed before death,[3] but so far none have been reported showing the effect of deep roentgen-ray therapy on these tumors. In this and doubtless in all the other cases, once the diagnosis was made it seemed useless to try any known form of treatment. However, in our case the patient was in great distress as a result of a very marked pericardial effusion (figure 1), and though we

* Received for publication May 15, 1939.
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† Solomon Strouse, in his recent article,[2] pointed out that we had erred in giving Pavlowski credit for the first diagnosis of a primary tumor of the heart. It seems that Pavlowski discovered his tumor at the time of autopsy and "reasoned backward from the autopsy protocol and showed how and why these symptoms were produced." Wallace Yater, whose recent excellent article [3] was also in error on this point, restudied these reports at my request and was able to confirm Strouse's statement. Strouse also cited the report by Barnes et al.[4] of a rhabdomyosarcoma of the heart. The tumor was discovered first in the deltoid muscle, and later developments led to the diagnosis of a tumor of the heart. Since this tumor was first discovered outside the heart, their case was regarded as an entirely different diagnostic problem.

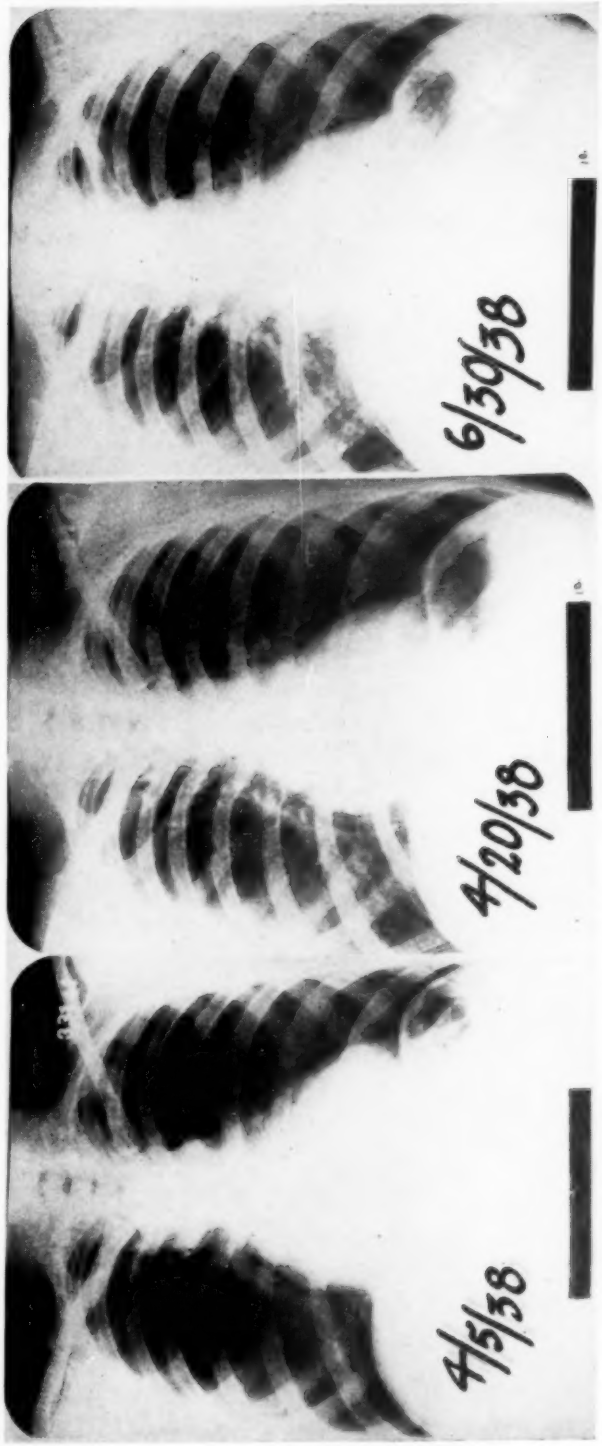

FIG. 1. This clearly shows the changes in the size of the heart shadow before and after roentgen-ray treatment. The cardiac diameter on April 5, 1938, was 18.8 cm., on April 20, 1938, 15.9 cm., and on June 30, 1938, 15.3 cm. The last film shows the beginning of the recurrence in the mediastinum.

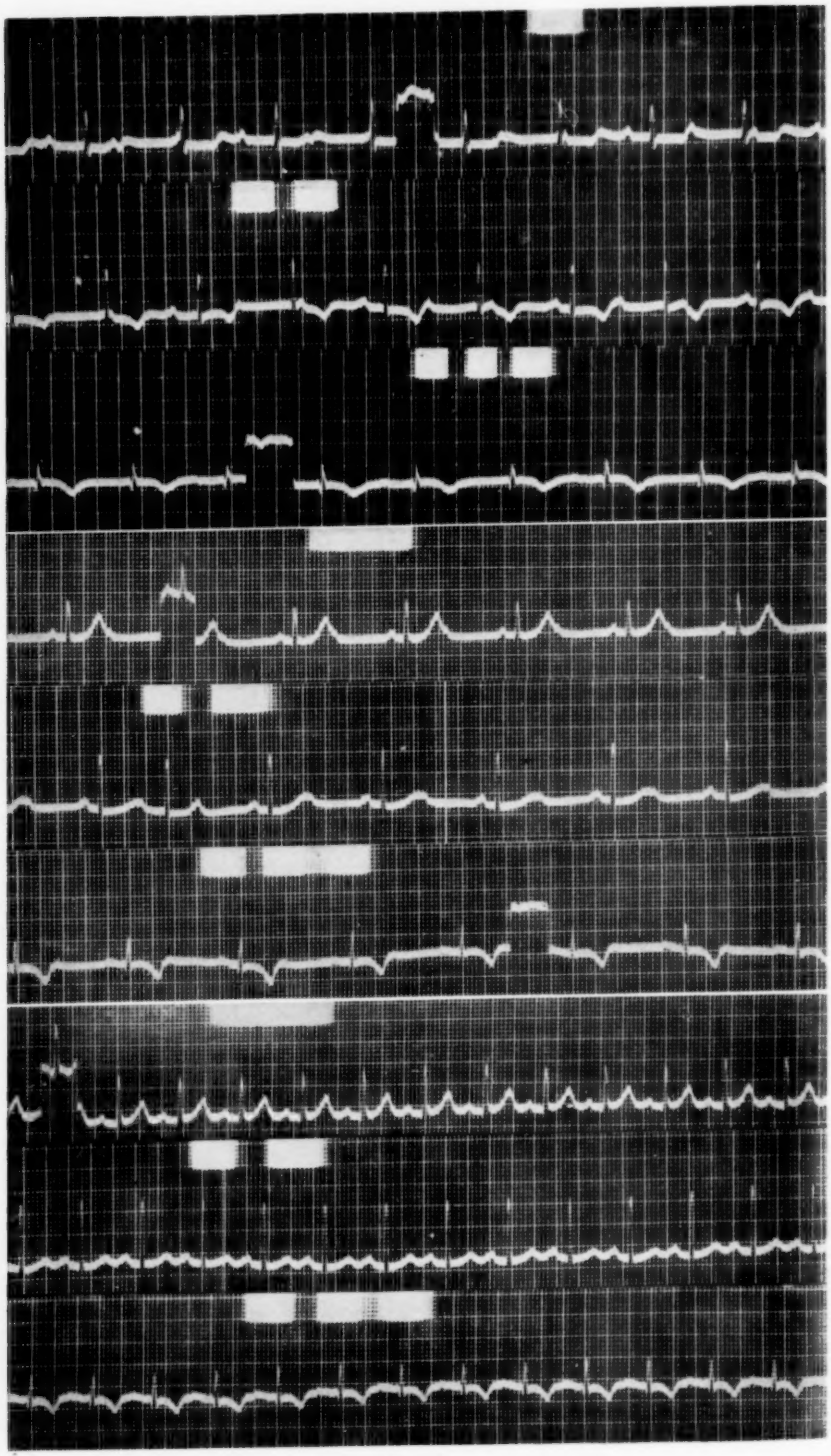

FIG. 2.

felt sure he would not recover entirely from his tumor, we hoped that the roentgen-ray treatment would relieve the symptoms of the pericardial effusion. Our hopes of helping him were dampened by the presence of a complete heart-block shown in the electrocardiogram, clearly indicating deep invasion of the heart by the tumor. However, the result was extremely gratifying. The effu-

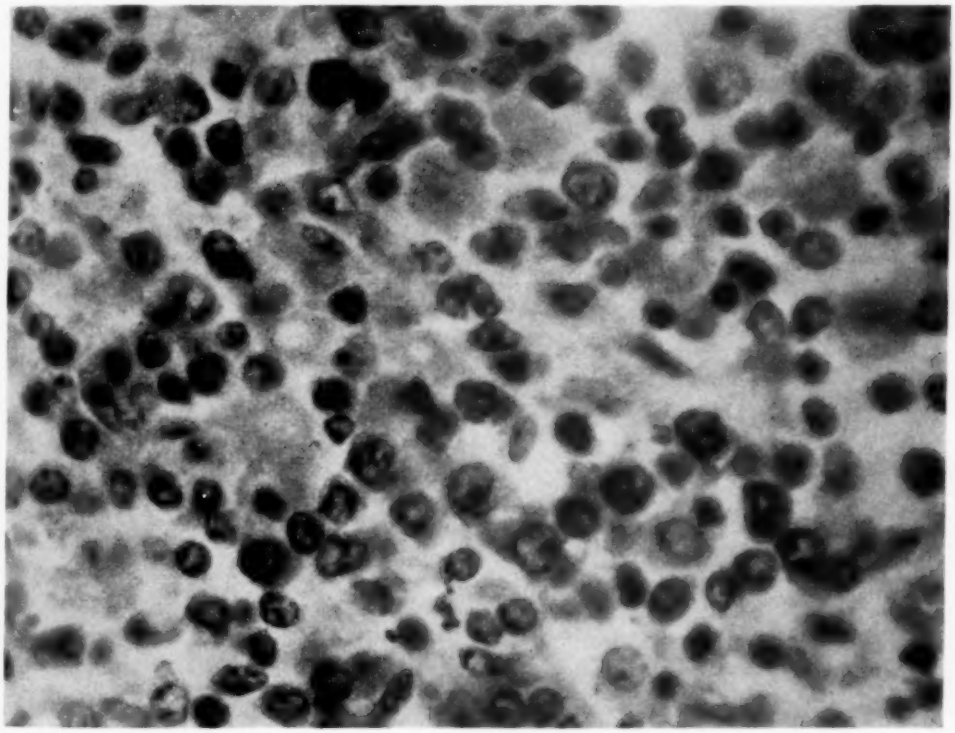

FIG. 3*a*. Microphotograph of sections of tissue removed from the cranium in July 1937.

sion completely disappeared and, curiously enough, the complete heart-block (figure 2) also disappeared, which led us to believe that at least a portion of the tumor in the intraventricular septum had been destroyed. The man was able to get out of bed and return to his regular work for about two months, and expressed extreme gratitude that he was given this respite. He subsequently died with the typical symptoms and findings of extensive secondary mediastinal tumor. Tissue sections of the original tumor, which arose in his skull or dura, and the first metastatic lesion in the neighboring lymph node were studied (figure 3). Cells typical of this tumor were found in the pericardial fluid (figure 3). The presence of these cells in the aspirated pericardial fluid, plus the immediate complete disappearance of the fluid and of the a-v block following roentgen-ray

FIG. 2. Electrocardiographic tracings showing the change from complete a-v block to 2:1 block, to normal mechanism, and the changes in T_1 and T_2. The change from complete block to 2:1 block first appeared on April 14, 1938, and the T-waves became upright about the same time. The depression in the S–T intervals in Leads I and II are probably too small to be of significance.

therapy, and the subsequent death with mediastinal tumor are adequate proof of the presence of the tumor in the pericardium and in the heart. There was no evidence of tuberculosis, rheumatic fever, nor syphilis. Unfortunately, an autopsy was denied. A most interesting series of electrocardiograms showing the change from complete heart-block, to partial heart-block, to normal mechanism

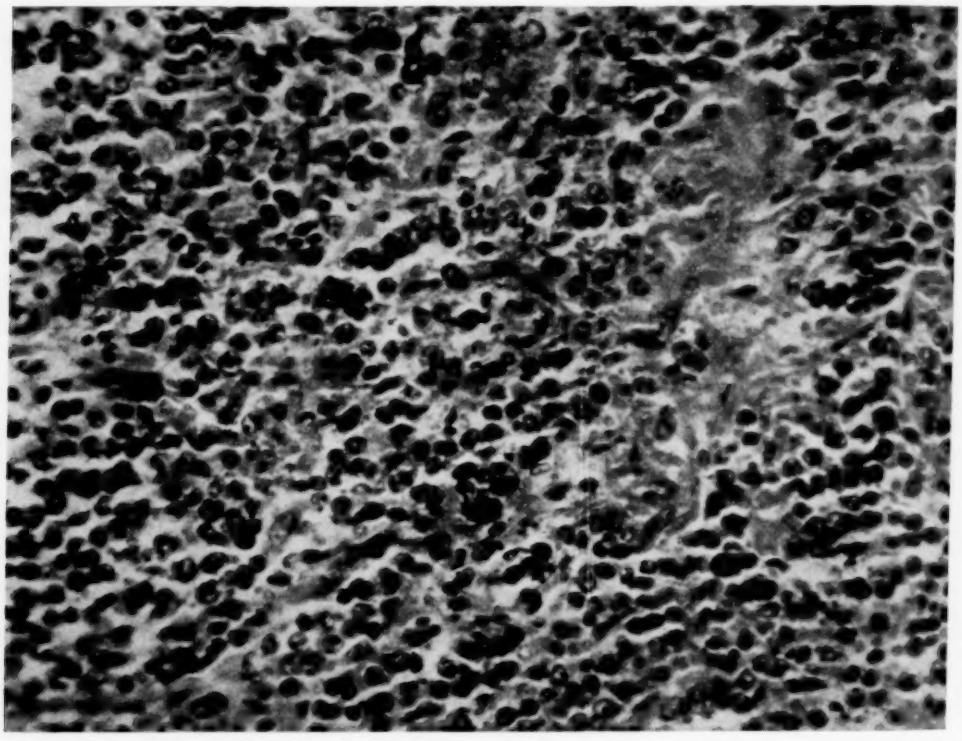

FIG. 3*b*. Microphotograph of sections from a lymph node near the right parotid gland removed in February 1938.

is included in this report (figure 2). The tracings also show the rapid changes in T-waves, etc., associated with the disappearance of the pericardial effusion. These T-wave changes were not due to the small amount of fluid aspirated from the pericardial sac, as the changes did not occur until 10 days later. In order to show these changes more clearly, a tracing was made almost every day, before and after the treatment, until the mechanism returned to normal. A study of these daily tracings shows that the first change from complete dissociation to 2:1 block occurred on April 14, 1938, nine days after roentgen-ray treatment was started, and that the return to normal mechanism was first recorded on May 11, 1938, 36 days after the onset of roentgen-ray therapy (figure 2). Lead IV was taken each time but was omitted from this figure for the sake of brevity, as it showed the usual upright T-waves and did not change.

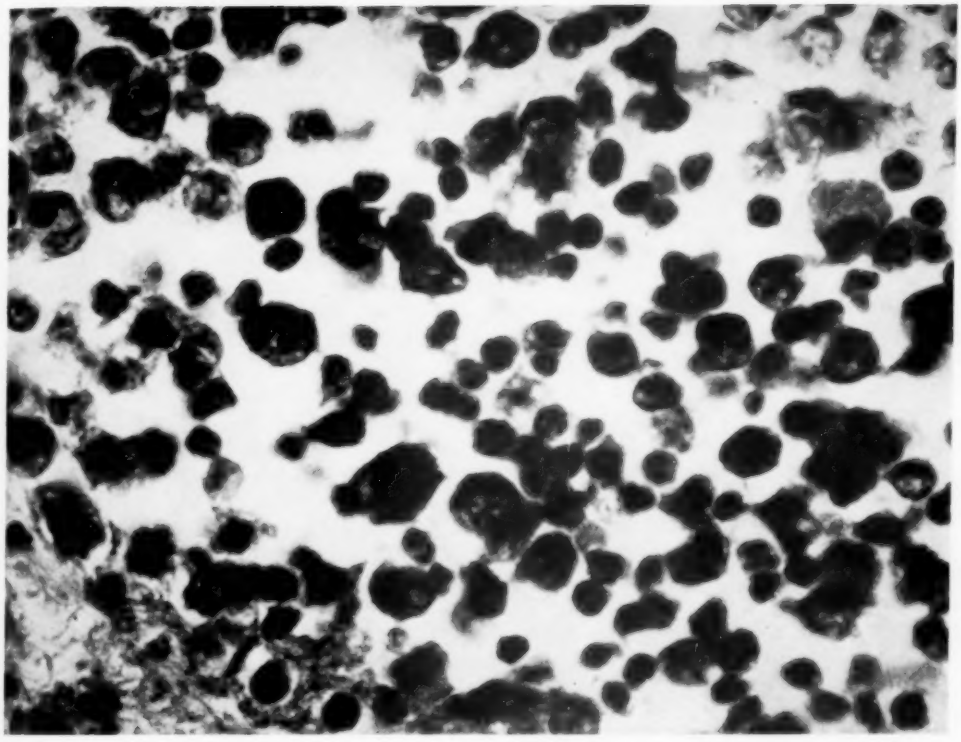

FIG. 3*c*. Microphotograph of sections of cells in the pericardial fluid April 4, 1938.

CASE REPORT

G. R. was a married, Polish Jewish, cotton importer, aged 28, who was seen first by Dr. Howard Aronson on March 15, 1938. He was in bed and complaining of fever, malaise, attacks of nausea, and dyspnea.

This patient gave a history of the development of a tumor over the right parieto-frontal region of his skull in July 1937. In August 1937, Dr. Harry Mock of Chicago, where the patient was living at that time, removed the tumor, including a large bone flap from this area, and then gave him a course of deep roentgen-ray treatment. Dr. Mock thought that the tumor arose from the dura, and microscopic sections (figure 3) were studied by Dr. E. F. Hirsch, who expressed the opinion that the tumor was a dural sarcoma. The patient felt very well until early February 1938, when he developed a recurrence in the region of the parotid gland which Dr. Mock removed; and roentgen-ray treatment was again administered over the region. He improved again and came to Dallas to carry on his work. About March 15 he began to have fever every day, reaching about 102° F. in the afternoon, as well as attacks of nausea and dyspnea. Efforts to determine the cause of the fever were not rewarded with success until a film of the chest was made, at which time the pericardial effusion was found. The lung fields were clear. On reviewing this history we felt certain that we were dealing with a metastatic tumor of the pericardium. Since these metastatic tumors frequently invade the septum, an electrocardiographic tracing was made on our first visit together in his home on April 4, 1938. This tracing (figure 2) showed a complete a-v dissociation which we felt furnished further positive evidence of the presence of the tumor.

Physical examination at this time showed a well nourished and developed, highly intelligent young man. The blood pressure was 118 systolic and 82 diastolic, temperature 100.2° F., pulse 90, respiration 20. He had a large bone defect in the right side of his head and a scar over the parotid area. There was slight cyanosis of the lips, and in a half reclining position he showed that most characteristic sign of pericardial effusion, distention of the veins of the neck, in a patient able to lie flat in bed comfortably. There was some widening of the cardiac area of dullness and slight but very definite muffling of the heart sounds. The lungs were clear, and the liver and spleen were not palpable; there was no dependent edema.

He was removed to the Baylor Hospital where about 50 c.c. of fluid were aspirated from his pericardial sac. No organisms were present in the fluid and the culture showed no growth after two weeks. The cell count was 16,150 per cu. mm. The fluid did not coagulate on standing. This fluid was carefully centrifuged for a long period and the sediment imbedded in paraffin. Sections of this were made and stained with hematoxylin, and eosin, and also with Wright's stain. These cells were studied by Dr. J. M. Hill, and Dr. George T. Caldwell, Professor of Pathology, Baylor University Medical School, whose report follows:

"Microscopic examination of sediments from pericardial fluid shows numerous peculiar cells of a wide variety of type. These cells vary greatly in character. First of all we find numerous lymphoid cells, moderate numbers of mononuclear cells and a few eosinophiles. The most interesting feature, however, is the presence of fairly numerous, rather large hyperchromatic cells, sometimes having fairly prominent nucleoli. We occasionally find mitotic figures in these cells. There are also a few scattered giant cells, sometimes appearing multilobed and sometimes multinucleated. No definite groupings of these abnormal cells are seen."

These slides, as well as the sections from the original tumor and from the metastatic tumor from the lymph node in the region of the parotid, were submitted by one of us (S. A. S.), on May 5, 1938, to Dr. S. B. Wolbach, Professor of Pathology of Harvard University Medical School. He stated that the cells in the pericardial fluid were unquestionably tumor cells, doubtless the same as those of the original tumor, and he expressed the opinion that the tumor was a type of myeloblastoma probably arising in the medullary portion of the frontal bone (figure 3).

The other laboratory studies were not very significant. The Wassermann was negative. The blood count was: hemoglobin 100 per cent or 15.3 gm., red blood cells 4,950,000, white blood cells 5,480, with 82 per cent polymorphonuclear cells (13 band forms), 17 per cent lymphocytes and one eosinophile. The urine was quite normal, with a specific gravity of 1.022.

The tumor had shown great sensitiveness to roentgen-ray therapy, so we had reason to believe that we could relieve the symptoms of the pericardial effusion by resorting to this form of treatment. The patient was referred to Dr. C. L. Martin, of Baylor Hospital, who gave him daily exposures to roentgen-rays, by a modified Coutard technic, for two weeks starting on April 5, 1938.*

The changes in the electrocardiograms before and after treatment are very well shown in figure 2. A complete heart-block is present on the tracing taken on April 4, 1938, as well as an inversion of T_2 and T_3, and a diphasic T_1. The tracing of April 20, 1938, shows typical 2:1 block and the reversion toward normal T-waves. The tracing of May 11, 1938 shows the return to the normal mechanism and normal T-waves. The roentgen-ray of the heart taken on April 4, 1938, shows a diameter of the heart of 18.8 cm.; on April 20, 1938, the diameter was 15.9 cm., and on June 30,

* Between April 7, 1938, and April 20, 1938, the patient received 1800 r measured in air, delivered to each of two areas measuring 15 cm. on a side laid out over the anterior and posterior aspects of the cardiac region. The daily dose was 300 r and the factors were 200 Kv., 25 Ma., a filter of 3/4 mm. of copper, and 1.0 mm. of aluminum, and a target skin distance of 50 cm. The output of the tube was 40 r per minute.

1938, it was 15.3 cm. (figure 1). The last film shows the recurrence of the tumor in the mediastinum.

The patient continued to have the fever, which he had had for three weeks, until the fifth day after roentgen-ray therapy was begun. He had no fever after that until the onset of the terminal episode four months later. The attacks of nausea persisted for about seven days. Roentgen-ray therapy was completed on April 20, 1938, and he was allowed to return to work a few days later. At this time he had no symptoms, but he was advised to refrain from any unusual exertion. He went about his work fairly well until June 21, 1938, when he developed a definite recurrence in the right side of the neck which disappeared soon after the institution of roentgen-ray therapy to this region. A mediastinal invasion was discovered on June 28, 1938, and he returned to Chicago for the duration of the summer, planning to take further treatment there. However, the tumor persisted and increased despite treatment, and the patient died of mediastinal compression on September 27, 1938, in St. Luke's Hospital, Chicago. There were marked dyspnea and extensive edema involving the neck, both arms and hands, and the upper portion of the body.

Comment

Metastatic tumors of the heart are not very rare, as they occur in approximately 0.5 per cent of cases of malignancy, and they are often easily recognized before death. This is particularly true when a pericardial effusion occurs in a patient with a known malignant tumor, or when such a case shows some form of heart-block in the electrocardiogram. These are the two ways in which the diagnosis has been made most commonly. Occasionally the diagnosis is made by a bizarre appearance of the heart shadow on the roentgen-ray film. The subject of this report had a primary tumor of the skull and both a pericardial effusion, with typical tumor cells in the fluid, and a complete heart-block, as shown in the electrocardiogram. He had a highly malignant tumor, probably a myeloblastoma which arose in the cranium, and which finally caused his death by a mediastinal compression.

He was subjected to deep roentgen-ray therapy according to a modified Coutard technic, with the hope of relieving some of his distress. We were amazed and gratified by the effectiveness of this treatment. The portion of the tumor invading the heart and pericardium must have been largely destroyed by the roentgen-rays, as the effusion vanished, and, to our surprise, the heart-block disappeared leaving a normal cardiac mechanism. As far as we can tell, this did not recur in these areas, though the time for recurrence was short, as the patient died of mediastinal compression about five months later.

Probably the most convincing sign of the efficacy of the roentgen-ray therapy was in the change from complete block to 2 : 1 block, then to normal mechanism. The change to 2 : 1 block occurred on the ninth day after the onset of treatment. The change in the T-waves, which probably indicated pronounced decrease in the pericardial effusion, occurred about the same time. This is confirmed by the decrease in the heart shadow on the roentgen-ray film observed on the fifteenth day after treatment.

It is doubtful at the present time that these observations are of any real value to patients with malignant tumors invading the heart. They do prove that the roentgen-rays will destroy tumors deep in the heart without any obvious effect on the function of the heart muscle.

SUMMARY

This is a report of a malignant tumor, invading the pericardium and the septum of the heart, which was treated by deep roentgen-ray therapy. There was strong evidence that the tumor was largely destroyed and that the function of the heart was not impaired by the treatment. The roentgen-ray films of the heart, the electrocardiographic tracings, and the microphotographs of the tissues are presented. They show the interesting sequence of events following roentgen-ray treatment of the tumor in the heart.

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EDITORIAL

GERONTOLOGY

GERONTOLOGY, which is the science of aging, is no longer of mere academic interest, but presents innumerable significant questions urgently demanding study and solution. Aging is a continuous biologic process which commences immediately upon the creation of a new individual and continues until death. Therefore, gerontology crosses the pathways of thought of all biologic sciences and presents problems at all ages. In this, gerontology differs conspicuously from geriatrics which has been defined as "that branch of medical science which treats of the *aged* in their physiologic and pathologic relations." Thus geriatrics is concerned with the consequences of senescence, the end result of senility, whereas gerontology includes in its domain of thought the processes of involution and senescence from conception onward.

Why have the problems of aging become so urgent? Surely aging is no recent phenomenon! The ancient Greeks were much concerned with the philosophy of the aged and Cicero orated with both passion and compassion upon the problems of the senescent. But the aged then were few and far between; careful estimates place the average duration of life of the ancient Roman citizen at from 20 to 30 years. Life expectancy increased slowly for many centuries and it is only in the last fifty years or so that conspicuous changes have occurred. In 1850 life expectancy in New England was but 40 years. By 1900 longevity in the United States had risen to 48 years, but since then the advance has been dramatic. By 1930 it had increased to over 60 years of age. The studies of Dublin[1] reveal the following significant figures: In 1900, 46 per cent of the total population of the United States was under 20 and but 17 per cent exceeded 45; in 1940 the youth under 20 are 34.7 per cent and those over 45 constitute 26.5 per cent of the population. By projection, it is conservatively estimated that in 1980, only forty years hence, only 26 per cent of the population will be youths under 20 and that those over 45 will include more than 40 per cent of our people.

The nation is aging rapidly. The virile, violent, but short-lived days of pioneering are largely passed. The future holds promise of profound changes. Urgent and unanswered problems arise in economic, political, sociologic, and psychiatric fields as well as in medicine. The children of today will be the elderly of tomorrow. The direction of some of the problems is already indicated. The clamor of the aged for economic security is heard throughout the breadth of the land. Even fantastic schemes such as those of Townsend are fanatically advocated. The problem of employment of older men demands serious attention. The grim specter of war

[1] DUBLIN, L. I.: Chapter 6 in COWDRY's "Problems of aging," 1939, Williams & Wilkins Co., Baltimore.

may accelerate these crucial problems; the mortality of war is largest among the youthful. There is no end to the list of problems and only a very meager beginning has been made toward their solution. The potentialities of the senescent for service have been barely touched. Accomplishments of such men as Oliver Wendell Holmes, W. H. Welch, Goethe, Edison, Titian, and many others in the evening of their lives are mere indicators of the vast storehouse of latent treasure existent in those so often sneeringly dubbed "old men." The judgment and experience of mature and highly trained minds are invaluable national assets. In times of stress and emergency it is upon the older shoulders that the greatest responsibilities rest. Conservation of such precious resources is a major responsibility of gerontology.

The medical implications of this fundamental shift in the age and character of the national population are many. The remarkable increase in longevity is due largely to improved preventive medicine and effective pediatrics. The saving of life in infancy and childhood, the control of infective diseases such as typhoid fever, smallpox and the like, have made possible the extension of life expectancy. As a consequence, the incidence of the so-called degenerative disorders, or those whose frequency rises sharply in later life, has increased conspicuously. Cardiovascular-renal disease, cancer, diabetes mellitus, arthritis, and cerebral accidents are replacing infective diseases as the most common causes of death. These are all chronic and progressive disorders, usually insidious of onset and silent until disability causes premature arrest of activities. Though we are learning much about therapeutic control of these disorders, honesty compels admission that cure and prevention are desiderata as yet unobtainable.

These disorders are not amenable to mass prevention as are infectious diseases. Preventive medicine must become individualized. Extension to mature adults of the wise pediatric policy of keeping children in the best of health by personal health maintenance programs is necessary if we hope to stem the rising tide of disability among those past the meridian. To be effective in health maintenance, medicine needs more precise methods of evaluating health than are available today. Though accuracy in diagnosis of disease has made immense advance, the mensuration of health is a wholly different problem. We can no longer say that health is the mere absence of obvious disease. Health evaluation involves the measurement of functional reserve capacities. These change with age. Normal is not a fixed point but a variable affected by age. The normal must be known and appreciated before the abnormal can be interpreted intelligently.

Senescence can not be measured by chronologic age. Physiologic age is not synonymous with chronologic age! Physiologic time [2] does not progress uniformly but varies its pace in different individuals, at different periods in the same individuals, and in the aging of different functions and structures. Criteria for the evaluation of physiologic age in man are

[2]. CARREL, A.: Physiological time, Science, 1931, lxxiv, 618. DUNOÜY, PIERRE: Biological time, 1937, Macmillan, N. Y.

urgently needed by clinical medicine. Undoubtedly no single criterion can ever suffice but physiologic studies intended to reveal depreciation in functional capacities may prove illuminating. The years from 40 to 60 are probably the most significant period for the application of prophylactic geriatrics which has for its objective not the prolongation of life beyond the basic limits set by species inheritance, but the maintenance of health and usefulness until senility really equals infirmity. Much more can be accomplished with the aging than for the aged. The two major obstacles are lack of accurate knowledge and man's perversity in ignoring prophylactic measures if they involve the slightest effort on his part. These obstacles are not insurmountable. The science of medicine can remove the first and the art of medicine can overcome the latter.

Gerontology, however, encompasses far more than the questions engendered by clinical study of "normal" aging in man and the disorders characteristic of later life. Improvement of clinical practice in prophylactic geriatrics is dependent largely upon advances in knowledge concerning the fundamental biologic processes of senescence. All living things age. Critical data anent the phenomena of aging may, therefore, be derived from studies of many diverse forms. The disciplines of botany, bacteriology, genetics, zoölogy, and all the many methodological subdivisions of the biological sciences are concerned with aging. There is great need for delineation and precise description of the structural, biochemical, and physiologic changes which constitute normal involution[3] or senescence. Paralleling such descriptive studies are needed investigations into the etiologic and pathogenetic factors involved. Experimental attempts at retarding or accelerating senescence may be expected to yield information illuminating the underlying mechanisms of aging. Though it is obvious that growth and tissue metabolism are greatly influenced by age, there is almost no precise information as to the manner of these relationships. Basic knowledge here may prove to be a key to the riddle of cancer. In brief, gerontology seeks to learn just what aging is, what it does, why it occurs, and what factors determine its rate and character.

In view of the extent and importance of this relatively unexplored science, it is gratifying to learn that the National Institute of Health, which is the research division of the U. S. Public Health Service, is now organizing and developing a new unit for research in gerontology. Though there are many scientists actively and significantly attacking the problems of aging, there has been no previous centralizing agency. The breadth of the field and the multiplicity of disciplines involved have prevented any comprehensive correlation of the many diverse investigations. Therefore, the first service this new unit is undertaking is to conduct a survey of the present trends of active and contemplated investigations into the problems of aging in American scientific institutions. This survey is intended to ascertain

[3] WARTHIN, A. S.: Old age: The major involution, 1929, Paul B. Hoeber, Inc., N. Y.

just what problems are being studied and the methods of approach being applied. It is highly probable that many investigations which do not pertain directly to aging will, nevertheless, yield data significant to the science if looked upon from a broad viewpoint. Inquiries regarding studies related to aging are being sent to scientists in the basic biologic sciences as well as to clinical investigators. From the clinical point of view the survey is concerned especially with those studies dealing with health evaluation, mensuration of functional capacities as criteria of physiologic age, and those diseases whose incidence rises sharply in later life.

Critical analysis of the information elicited by such a survey may be expected to serve several valuable purposes. It should assist in bringing together in closer coöperation investigators interested in related problems, especially when widely divergent methods of approach are being utilized. The survey will likewise emphasize the urgent need for greatly augmented support for significant studies of these vitally important problems of senescence. The broad and general pattern of the problems being investigated will undoubtedly reveal a number of neglected "blank spots" which may justify special emphasis in the future. Analysis of the data of the survey will also be an invaluable aid in formulating future research programs.

E. J. S.

BOOK REVIEWS

Endocrine Therapy in General Practice. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P. 192 pages; 21 × 15 cm. The Year Book Publishers, Inc., Chicago. 1938. Price, $2.75.

This brief and concise book is written for the man in general practice. The author endeavors to explain the rationale in the present use of endocrine substances and to point out what can be expected from them. The individual products of the pharmaceutical houses are recorded by name and the recommended dose given. This in itself should prove of help to practicing physicians, many of whom are besieged by the detail men to such an extent that they are apt to become bewildered.

As is stated in the preface this work is in no sense encyclopedic in content. Nevertheless both gynecologists and endocrinologists can derive much benefit from reading it. For those who do not feel that the material presented is sufficiently comprehensive references for further reading are given at the end of many of the chapters. The book contains many photographs of patients. These illustrate the changes in bony contour and fat disbursements that occur with endocrine disturbances.

L. B.

Dermatologic Allergy; Introduction in the Form of a Series of Lectures. By MARION B. SULZBERGER, M.D. 540 pages; 23.5 × 16 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, $8.50.

The author holds a unique position in the field covered by this volume. He has greatly influenced the current attempt to classify and arrange those skin diseases known or believed to be the result of allergic processes. Dr. Sulzberger reveals a profound knowledge of his subject, a knowledge which combines a wide dermatologic experience with a thorough understanding of the subject of allergy.

The material is presented as a series of lectures, which are apparently those delivered by the author in his teaching. Usually, in the opinion of the reviewer, this is not the best way of arranging a text, but it serves Dr. Sulzberger's purpose satisfactorily because so much of his material has to do with a subject that is in a state of flux and consequently must be presented in a discursive and non-dogmatic fashion.

His use of the word "allergy" as an all inclusive term, including increased reactions of specific sensitivity and the decreased reactions of immunity, is at variance with the current use of the term but his arguments in favor of this use are quite persuasive.

The lecturer seeks to show the similarity between sensitivity resulting from infection and that resulting from non-living materials and does it very well. He differentiates between eczematous or contact type reactions, urticarial responses and those reactions resulting from sensitivity to infection.

He discusses in detail allergy to tuberculin, to fungi, to syphilis, to miscellaneous infections and to drugs in a clear and most interesting manner.

There are many who do not entirely agree with the author's conception of dermatologic allergy, but none ignore him. All the workers interested in allergy or dermatology have some opinion in the matter, being either for or against his conception.

The book is unique in its field and has served to crystallize a subject that has heretofore been vague in its outline. The reviewer feels justified in recommending it highly to those interested in this phase of medicine.

H. M. B.

Obesity and Leanness. By H. R. Rony, M.D. 300 pages; 24 × 15 cm. Lea and Febiger, Philadelphia. 1940. Price, $3.75.

A good book. The controversies in this complicated aspect of medicine are critically probed, in a factually explicit, even reportorial style. A generous sprinkling of the author's own studies is checked against the findings of others.

Beginning with an impartial evaluation of the problems and data of fat metabolism, the rôle of adipose tissue in the cycle is considered. Caloric balance as the sole cause of obesity is scouted. Dynamic and static phases of weight production are urged. The chapter on lipophilia is the best discussion of that concept this reviewer has seen, and a chapter on the nervous system and its relation to obesity is particularly good. Appetite and hunger are stressed rather more than seems justified, and the discussion of the intermediary metabolism is not sufficiently documented.

The references are good, and the chapter résumé particularly helpful. Emphasis on follow-up is well placed. With the avitaminoses assuming the proportions of a public health problem, this book should be required reading for all concerned with dietary and metabolic problems.

C. A.

Diseases of the Digestive System in Food Allergy. By Josef Smul, M.D. 219 pages; 22.5 × 15 cm. Medical Library Co., New York City. 1940. Price, $3.50.

This book is a collection of erroneous statements presented with complete solemnity. It is not only completely valueless but is actually potentially dangerous in that, in such conditions as gastrointestinal malignancies, it gives far-advanced findings as diagnostic criteria.

H. M. B.

The Diagnosis and Treatment of Diseases of the Esophagus. By Porter P. Vinson, B.S., M.A., M.D., D.Sc., F.A.C.P. 224 pages; 23 × 15 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, $4.00.

This textbook devoted entirely to diagnosis and diseases of the esophagus is an excellent contribution to the literature on this subject. The value of esophagoscopy as a means of diagnosis and treatment is stressed. The technic for its use is clearly described. The importance of studying related general symptoms before a diagnosis is made is emphasized.

Hysterical dysphagia, cardiospasm, esophagitis, diverticula, tumors and foreign bodies are carefully considered. A great deal of attention is given to the diagnosis and treatment of strictures of the esophagus. The technic of dilatation is well illustrated. Cancer of the esophagus is thoroughly discussed and methods of treatment outlined. The internist will find this book very valuable as a reference.

E. A. L.

Obstetrics and Gynecology. By the Departmental Staff of the University of Chicago and other contributors. Edited by Fred. L. Adair, M.A., M.D., F.A.C.S. Vol. I: 1000 pages; Vol. II: 1031 pages, 24 × 15 cm. Lea and Febiger, Philadelphia. 1940. Price, $20.00.

This work represents the combined judgment of the members of the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital, because no names are associated with the individual chapters. The Editor considers obstetrics and gynecology one specialty, advocates the combination of these two fields, and has arranged the subject matter with this concept in view. He states that since obstetrics is of major importance, the larger portion of the work is devoted

to that field. He also states that the work is not primarily intended for a reference, but designed for the medical student and the practitioner of obstetrics and gynecology. The reviewer is of the contrary opinion because of the size of the work, the statistical data presented, the numerous charts, the historical chapters, and chapters correlating obstetrics and gynecology with other fields, all of which stamp it as a reference work; and because medical students will probably use such a work as a reference rather than as a text. In addition, the usual text does not attempt to give such a full account of the medical, social and economic importance of human reproduction as is found here. The chapter on obstetric morbidity and mortality establishes the work as a reference in the opinion of the reviewer. Principles are stressed and the fields of obstetrics and gynecology and biology and medicine in general are correlated.

The material dealing with pathology throughout the work is unusually well presented, and accompanied by excellent illustrations. For the practitioner there is a chapter on obstetrics in the home which includes valuable suggestions on the diagnosis and management of the more dangerous complications. In a work presented as a text the reviewer was surprised to find so little space devoted to the common obstetrical and gynecological operations with very few illustrations of some of the common procedures with which the student and practitioner must be familiar.

Interesting data relative to history, laws and customs are to be found. There is a timely chapter on the relationship of infection and immunity to reproduction. Biology and problems of reproduction and the relationships of the basic sciences and clinical medical sciences to obstetrics and gynecology are fully considered. Of special interest to readers of this journal is the chapter on internal medicine in relation to obstetrics and gynecology, in which the field is well covered. There is a valuable chapter on puerperal infection with instructive case histories appended. There are seven chapters devoted to the newborn and to pediatrics. The chapter on roentgen diagnosis in obstetrics and gynecology is interesting and well illustrated.

The volumes are large and each has a convenient ribbon bookmark. There is an index for both volumes at the end of each. The type is clear and the style pleasantly readable. The illustrations are excellent and for the most part original though rather few in number. There is a valuable appendix concerning dietetics, laboratory methods, and vital statistics. The list of references occupies 25 pages and is found in volume 2. The references are arranged alphabetically by author, and frequently only the specific journal reference is given with no title of the article. This does not appear to the reviewer as practical and efficient a method as that in which they are given under subject headings or at the end of each chapter.

The work represents a significant contribution to obstetrics and gynecology and the growing tendency toward the combination of these fields for the purpose of "improved service, teaching and research." This is an elaborate work and the Editor and his associates should be congratulated upon the successful completion of so great a task. It undoubtedly is a work which every practitioner of obstetrics and gynecology will find profitable.

J. E. S.

COLLEGE NEWS NOTES

A. C. P. Committees and Regents to Meet

By direction of the President, the various Committees and the Board of Regents of the College will meet at the College Headquarters in Philadelphia, December 14–15, 1940, for the transaction of the regular mid-year business.

Among many important matters to be considered will be the statement of operation, the adoption of 1941 budgets, election of candidates to membership, the selection of the recipient of the John Phillips Memorial Award for 1941, adoption of the program of postgraduate and refresher courses for 1941 and final arrangements for the Twenty-ninth Annual Session of the College in Boston.

Gifts to the College Library

The following gifts to the College Library of publications by members, recently received, are gratefully acknowledged. It is with particular gratification and deep appreciation that the donation of so many books by College members is here recorded.

The inspiration for the forming of a library of books, of which members of the College are the authors, grew out of an act of courtesy and thoughtfulness of a few years back when a member presented his autographed book to the American College of Physicians. The Library, in a sense, is intended to be a *memorial library* to our members. A general medical library, other than one of this character, would scarcely be justified at the College Headquarters, due to the availability of so many general medical libraries in Philadelphia. The College library of books has a growing interest and increasing value and will have a deeper sentiment as the years pass by.

Fellows of the College constitute a group of the most productive medical men of America. Books they have written occupy in many institutions a forefront position in American medical literature. Authors who are members of the College are especially invited to donate autographed copies of their books to this Library. Gifts will be promptly acknowledged both personally and through this journal. Appropriate bookplates, giving date of receipt and name of donor, are attached, and the books are properly indexed and added to the Library.

Books

Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa., "Diabetes—Self Help for the Diabetic";

Dr. David P. Barr, F.A.C.P., St. Louis, Mo., "Modern Medical Therapy in General Practice," Volumes I, II, and III;

Dr. Albert G. Bower (Associate), Glendale, Calif., "Communicable Diseases for Nurses";

Dr. Linn J. Boyd, F.A.C.P., New York, N. Y., "Cardiovascular Diseases—Their Diagnosis and Treatment" and "Clinical Electrocardiography";

Dr. William B. Castle, F.A.C.P., Boston, Mass., "Lectures on the Anaemias and Vitamin Deficiencies";

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., "A Textbook of Medicine by American Authors," 5th edition;

George Washington University School of Medicine, Washington, D. C., "Studies from the School of Medicine, George Washington University, for 1939–1940";

Dr. Sigmund S. Greenbaum, F.A.C.P., Philadelphia, Pa., "Diseases of the Mouth and Their Treatment," 2nd edition;

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, "Principles of Hematology," 2nd edition;
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., "Simplified Diabetic Management," 3rd edition;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa., "Management of the Cardiac Patient";
Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., "Clinical Heart Disease," 2nd edition;
Dr. Robert L. Levy, F.A.C.P., New York, N. Y., "Nomenclature and Criteria for Diagnosis of Diseases of the Heart";
Dr. Arthur M. Master, F.A.C.P., New York, N. Y., "The Electrocardiogram and X-Ray Configuration of the Heart";
Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., "Endocrine Therapy in General Practice," 3rd edition;
Dr. Torald Sollmann, F.A.C.P., Cleveland, Ohio, and Dr. Paul J. Hanzlik, F.A.C.P., San Francisco, Calif., "Fundamentals of Experimental Pharmacology," 2nd edition;
Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., "Beyond the Clinical Frontiers";
Dr. James J. Waring, F.A.C.P., Dr. Abe Ravin (Associate), and Dr. Edward G. Billings (Associate), Denver, Colo., "Directions for Examining Patients."

Reprints

Dr. J. Edward Berk (Associate), Philadelphia, Pa.—3 reprints;
Dr. Belford C. Blaine (Associate), Pottsville, Pa.—2 reprints;
Dr. Leon L. Blum (Associate), Terre Haute, Ind.—1 reprint;
Dr. Henry O. Colomb, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Joseph Edeiken (Associate), Philadelphia, Pa.—1 reprint;
Dr. William Freeman, F.A.C.P., Worcester, Mass.—2 reprints;
Dr. Thomas N. Hunnicutt, Jr. (Associate), Newport News, Va.—1 reprint;
Dr. Henry Pleasants, Jr., F.A.C.P., West Chester, Pa.—2 reprints;
Dr. Henry M. Ray, F.A.C.P., Pittsburgh, Pa.—1 reprint;
Dr. William S. Reveno, F.A.C.P., Detroit, Mich.—1 reprint;
Dr. R. Henry Temple (Associate), Kinston, N. C.—1 reprint;
Dr. Morris M. Weiss, F.A.C.P., Louisville, Ky.—3 reprints;
Dr. Willard R. Wirth, F.A.C.P., New Orleans, La.—1 reprint;
Dr. Mast Wolfson, F.A.C.P., Monterey, Calif.—1 reprint;
Dr. S. E. Wolpaw (Associate), Cleveland, Ohio—2 reprints.

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows: For further details and application forms communicate with the respective secretaries.

American Board of Internal Medicine:
William S. Middleton, M.D., Secretary
1301 University Ave.
Madison, Wis.

Written Examination, February 17, 1941.
Oral Examination, Boston, April, 1941, in connection with meeting of the American College of Physicians.
Oral Examination, Cleveland, June, 1941, in connection with meeting of the American Medical Association.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: C. Guy Lane, M.D., Secretary 416 Marlboro St. Boston, Mass.	Oral Examination, Chicago, December 6–7, 1940. Applicants classified in Group B take both the written and oral examinations; applicants classified in Group A take the oral examination only.
AMERICAN BOARD OF PATHOLOGY: F. W. Hartman, M.D., Secretary Henry Ford Hospital Detroit, Mich.	Cleveland, June, 1941, in connection with the meeting of the American Medical Association.
AMERICAN BOARD OF PEDIATRICS: C. A. Aldrich, M.D., Secretary 723 Elm St. Winnetka, Ill.	New York City, March 30–31, 1941, immediately following the Region I meeting of the American Academy of Pediatrics. Chicago, May 18, 1941, immediately following the Region III meeting of the American Academy of Pediatrics.
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N. W. Washington, D. C.	New York City, December 18–19, 1940.
AMERICAN BOARD OF RADIOLOGY: B. R. Kirklin, M.D., Secretary 102 Second Ave., S. W. Rochester, Minn.	Cleveland, June, 1941, in connection with meeting of the American Medical Association.

On September 18 Dr. Edward L. Bortz, F.A.C.P., was inducted as President of the Philadelphia County Medical Society. Dr. Rufus S. Reeves, F.A.C.P., was the retiring President and Dr. Louis H. Clerf, F.A.C.P., is the President-Elect.

The 1940 Graduate Fortnight of the New York Academy of Medicine was held in New York City October 14–25. The subject of this Fortnight was "Infections." Dr. Charles F. Tenney, F.A.C.P., New York, was Chairman of the Committee on Panel Discussions, and Dr. F. Warner Bishop, F.A.C.P., New York, was Chairman of the Committee on Hospital Clinics.

Dr. Christopher C. Shaw (Associate), Bellows Falls, Vt., has been commissioned a Lieutenant Commander in the Medical Corps of the United States Naval Reserve.

Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I., has been appointed a member of the new Basic Science Board for the State of Rhode Island for a term of two years.

Among those who have been appointed to the Territorial Committee on Medical Preparedness by the Puerto Rico Medical Association, to work in coöperation with the state representative of the Committee on Medical Preparedness of the American

Medical Association, are:

Dr. Oscar Costa-Mandry, F.A.C.P., San Juan, Chairman
Dr. Manuel de la Pila Iglesias, F.A.C.P., Ponce
Dr. César Dominguez (Associate), Humacao

Dr. George Blumer, F.A.C.P., New Haven, Conn., was the guest of honor at a dinner in June, which was given to mark his retirement from active service at the Yale University School of Medicine. Dr. Blumer joined the staff at Yale as Professor of Theory and Practice of Medicine in 1906. He was the John Slade Ely Professor of Theory and Practice of Medicine from 1908 to 1920, and since 1920 he has been David P. Smith Clinical Professor of Medicine. Dr. Blumer served as Dean of the Medical School from 1910 to 1920.

Dr. Charles B. Sylvester, F.A.C.P., Portland, Maine, was elected President of the Maine Public Health Association at its 29th annual meeting in Kennebunk, July 11.

Dr. Robert J. Schneck, F.A.C.P., Detroit, Mich., has been appointed to the Public Welfare Commission of Detroit for a four year term.

Dr. Nathan B. Van Etten, F.A.C.P., President of the American Medical Association, New York, N. Y., addressed the ninth annual meeting of the Interstate Medical Association held in Chautauqua, N. Y., July 24. Other speakers at this meeting included Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, on "The Care of Anemia," and Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y., on "Self Medication and Its Dangers." Dr. Aaron, Dr. Louis Maxwell Lockie, F.A.C.P., Dr. Clayton W. Greene, F. A. C. P., Dr. Francis D. Leopold, F. A. C. P., and Dr. Frank Meyers (Associate), all of Buffalo, N. Y., conducted a panel discussion on "Recent Advances in Therapeutics."

At the recent meeting of the Medical Society of Virginia, held jointly with the West Virginia Medical Association at White Sulphur Springs, W. Va., Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, Va., was elected one of the vice presidents.

Dr. Walter M. Boothby, F.A.C.P., Rochester, Minn., was one of the guest speakers at the 99th annual meeting of the State Medical Society of Wisconsin, which was held in Milwaukee, September 18–20. Dr. Boothby spoke on "Physiologic Problems Involved in Aviation."

Among the speakers at the annual meeting of the American Association for the Study of Neoplastic Diseases held in Washington, D. C., September 5–7, were:

Dr. Rollin H. Stevens, F.A.C.P., Detroit, Mich.—"Present Day Treatment of Neoplasia" and "What Experimental Biochemistry Suggests for the Future";
Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C.—"Tumor of the Thyroid Gland";

Dr. Aura J. Miller, F.A.C.P., Louisville, Ky.—" Epithelioma of the Labia, with Discussion of Methods of Treatment."

Dr. J. Howard Holbrook, F.A.C.P., College Governor for Ontario, Hamilton, was chosen President-Elect of the Canadian Tuberculosis Association at their annual meeting in Montreal in June.

The British Columbia Medical Association held its annual meeting in Nelson, B. C., September 9–11. Among the speakers at this meeting were:

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—" Deficiency States and Their Treatment " and " Problems Presented by the Jaundiced Patient ";
Dr. George H. Anderson, F.A.C.P., Spokane, Wash.—" Hyperventilation Syndrome."

The American Psychiatric Association held its second regional postgraduate institute at the Central State Hospital, Lakeland, Ky., September 23 to October 5, in coöperation with the division of hospitals and mental hygiene. Among the lecturers at this institute were Dr. S. Spafford Ackerly, F.A.C.P., Louisville, Ky., Dr. Lawrence Kolb, F.A.C.P., Washington, D. C., and Dr. Edward G. Billings (Associate), Denver, Colo.

The 35th annual meeting of the Tri-State Medical Society was held in Shreveport, La., September 25–26. Among the guest speakers at this meeting were:

Dr. George W. Parson, F.A.C.P., Texarkana, Ark.—" Interesting Cases of Tularemia ";
Dr. Homer E. Prince, F.A.C.P., Houston, Tex.—" Asthma—Practical Considerations ";
Dr. Silas C. Fulmer (Associate), Little Rock, Ark.—" Diagnosis of Heart Disease."

Among the guest speakers at the 18th annual clinical conference of the Kansas City Southwest Clinical Society, held in Kansas City, Mo., September 30 to October 3, were:

Dr. John T. King, F.A.C.P., Baltimore, Md.—" Relation Between Coronary Disease and Hypertension ";
Dr. Fred M. Drennan, F.A.C.P., Chicago, Ill.—" Diagnosis and Interpretation of Clinical Findings in Peptic Ulcer ";
Dr. Thomas Fitz-Hugh, Jr., F.A.C.P., Philadelphia, Pa.—" Interrelationship of Cholelithiasis and Coronary Artery Disease ";
Dr. James S. McLester, F.A.C.P., Birmingham, Ala.—" The Part Played by the Vitamins in Human Metabolism ";
Dr. James G. Carr, F.A.C.P., Chicago, Ill.—" Prognosis in Cardiac Disease ";
Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill.—" Management and Treatment of Obesity."

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on problems in gastroenterology at a meeting of the Ninth Councilor District in Marshfield, Wis., July 11.

Dr. Oscar Costa-Mandry, F.A.C.P., and Dr. Ramón M. Suárez, F.A.C.P., both of San Juan, P. R., have been appointed to the Executive Committee of the Inter-American Institute for Hospital Administrators.

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., spoke on "Recent Developments in Gastric Physiology" at the 51st annual meeting of the American Association of Railway Surgeons held in Chicago, September 16–18.

Dr. Elmer L. Sevringhaus, F.A.C.P., College Governor for Wisconsin, Madison, was one of the speakers at the 45th annual meeting of the American Academy of Ophthalmology and Otolaryngology held in Cleveland, Ohio, October 6–10.

The Connecticut State Medical Society held its 16th clinical congress in New Haven, Conn., September 17–19. Among the guest speakers were:

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass.—"Newer Developments in the Treatment of Diabetes";
Dr. Alvan L. Barach, F.A.C.P., New York, N. Y.—"Gas Inhalation Therapy."

Among the guest speakers at the 151st annual session of the Medical Society of Delaware held in Rehoboth Beach, September 9–11, were:

Dr. John A. Kolmer, F.A.C.P., Philadelphia, Pa.—"The Present Status of Vaccination Against Disease";
Dr. George C. Griffith, F.A.C.P., Philadelphia, Pa.—"The Significance of Precordial Pain";
Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa.—"Renal Aspects of Hypertension";
Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa.—"Atheromatous Cardiovascular Disease."

Dr. Oscar O. Miller, F.A.C.P., Louisville, Ky., gave the oration in medicine at the annual meeting of the Kentucky State Medical Association held in Lexington, September 16–19. The subject of Dr. Miller's address was "The Evolution of Our Knowledge of Tuberculosis."

The Michigan State Medical Society held its 75th annual session in Detroit, September 25–27, under the presidency of Dr. Burton R. Corbus, F.A.C.P., Grand Rapids. Among the guest speakers at this meeting were:

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C.—"Surgery of the Heart and the Heart in Surgery";
Dr. Arthur R. Elliott, F.A.C.P., Chicago, Ill.—"Arterial Hypertension: Forty Years in Retrospect";
Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn.—"Modern Trend in the Treatment of Syphilis";
Dr. John H. Musser, F.A.C.P., New Orleans, La.—"Vitamin and Mineral Requirements in Pregnancy and the Puerperium";
Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y.—"Medical and Surgical Significance of Avitaminosis";

Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill.—"The Primary Tuberculous Infection in Adults";
Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"Changing Picture of Diabetes."

Dr. Rufus I. Cole, F.A.C.P., Mount Kisco, N. Y., delivered the Andrew P. Biddle Oration at a public meeting of the Society, September 25.

The Jackson County Health Forum, sponsored by the auxiliaries of all the accredited hospitals of Jackson County, Mo., have announced the following program for 1940–41:

Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., October 16—"The Nature of Aging and the Chimera of Rejuvenation";
Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., November 20—"What's the Matter with the Patient Who Is Tired All the Time?";
Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., December 18—"The Effects of Narcotics and Alcohol on the Human Body: Facts, Not Opinion";
Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla., February 19—"Glandular Mechanism of the Body";
Dr. Bernard L. Wyatt, F.A.C.P., Tucson, Ariz., March 19—"Arthritis—the Great Responsibility and Opportunity."

Dr. Jack C. Norris, F.A.C.P., Atlanta, Ga., spoke on "Technical and Chemical Importance of the Erythrocyte Sedimentation Rates," and Lieut. Col. James E. Ash, F.A.C.P., (MC), U. S. A., spoke on "Bone Pathology" at the recent annual meeting of the Piedmont Postgraduate Clinical Assembly held at Anderson, S. C. Dr. Edgar A. Hines, F.A.C.P., Seneca, S. C., is President of the Assembly.

The Mississippi Valley Medical Society held its 6th annual meeting in Rock Island, Ill., September 25–27. Among the speakers at this meeting were:

Dr. Walter Lincoln Palmer, F.A.C.P., Chicago, Ill.—"The Diagnosis and Treatment of Gastric Diseases" and "Colitis—Functional and Organic";
Dr. Leon Unger, F.A.C.P., Chicago, Ill.—"Diagnosis and Treatment of Migraine";
Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—"Sulfanilamide and Its Derivatives";
Dr. David O. N. Lindberg, F.A.C.P., Decatur, Ill.—"Pulmonary Tuberculosis—Practical Points in Diagnosis and Treatment."

Dr. Unger conducted a private instructional course in "Allergy" and Dr. Volini, "The Treatment of Congestive Heart Failure."

OBITUARIES

DR. ELSWORTH S. SMITH

Dr. Elsworth S. Smith of St. Louis died on June 7, 1940, at the age of 76.

Dr. Smith was born in St. Louis, on January 1, 1864. He was the son of Dr. Elsworth Fayssoux Smith, one of the city's most influential physicians. Through his mother he was a direct descendent of Pierre Laclede, one of the founders of St. Louis. He received his bachelor of arts and master's degrees from St. Louis University and in 1887 graduated from the St. Louis Medical College. He interned at the St. Louis City Hospital, where he was later senior physician and assistant superintendent. In 1900 he entered the private practice of medicine and at about the same time associated himself with the Washington University School of Medicine, where he taught continuously for almost four decades and where for many years he was the Professor of Clinical Medicine. He was a member of the staff of Barnes Hospital from the time of its establishment and for many years previously had visited at the old Washington University Hospital. At one time or another during his life he had served on the staffs of the Mullanphy Hospital, the Barnard Free Skin and Cancer Hospital and the O'Fallon Dispensary.

In 1918 he was president of the St. Louis Medical Society and simultaneously was acting as chairman of the Fourth Medical Advisory Board of the Selective Draft Service and as a member of the Missouri Branch of National Defense. He was one time president of the American Congress of Internal Medicine. His interest and participation in the affairs of the American College of Physicians dated from the day of its founding.

One of the pioneer heart specialists of this country, he was throughout his life a contributor to the literature of circulatory diseases. Although he was nationally well known, it was in St. Louis that his influence was chiefly felt. As the son of a prominent physician and as a member of an old and influential family, he was given at an early age large responsibilities which from the beginning he undertook with modesty but fulfilled with distinction. Always a friend to younger colleagues, he retained throughout his life the intellectual eagerness of youth. Educated in an older school of medicine and living through a period of unprecedented changes in medical practice, he was ever alert to grasp and utilize newer ideas which might serve his patients or add value to his teaching. As a consultant he was superb, and his tempered judgment and sage advice were eagerly sought by his colleagues and by generations of his students. His devotion to his patients was a constant source of inspiration to all who saw him at work. Even during the last years of his life, when personal bereavement and failing health made his

own life more difficult, he continued to be available at any time of day or night to those who sought his help.

Elsworth Smith's death was mourned by hundreds of St. Louisans who for almost two score years had known him as physician, counselor and friend. To his colleagues it meant not only the loss of a well loved comrade but also the passing of one who perhaps more than any other personified the ethical standards and devotion of the physicians of the last century.

DR. PERCY MOREAU ASHBURN

Colonel Percy Moreau Ashburn was born July 28, 1872, in Batavia, Ohio, the son of Dr. Allen W. Ashburn. He received his early education in his native city, and graduated from the Jefferson Medical College of Philadelphia in 1893. Three years later Colonel Ashburn married Miss Agnes Davis, the daughter of the late Representative Frank Davis of Ohio. Upon the outbreak of the Spanish-American War he was appointed Contract Surgeon, U. S. A., and within a few months, upon his appointment as First Lieutenant and Assistant Surgeon, he sailed for the Philippine Islands where he took part in the 1899 campaign. During that year he was also executive officer and operating surgeon of the Santa Mesa and First Reserve Hospital in Manila.

Early in 1906 Captain Ashburn had the distinction, with Dr. Charles F. Craig (now Colonel Craig, U. S. A. retired), of organizing the Army Board for the study of tropical diseases in the Philippine Islands. The Board studied filariasis, yaws and dengue, and in that year discovered the method of transmission of the latter by mosquitoes.

In the following year Captain Ashburn was promoted to the rank of Major in the Medical Corps, and two years later he was made a member of the Commission to Liberia for the investigation of medical conditions there. In 1913 he was again detailed as member and president of the Army Board for the study of tropical diseases in the Philippine Islands, and at Ancon, Panama, in the following year became General Inspector of the Health Department in Panama.

In May, 1917, due to the expansion of the Army, Major Ashburn was made a Lieutenant Colonel, and almost immediately was promoted to be a full Colonel. In that year he was detailed as the Chief Medical Officer of the training camp at Fort Benjamin Harrison, going overseas in 1918. While with the American Expeditionary Forces Colonel Ashburn became a member of the commission to examine and report upon the treatment of German war prisoners in Bern. Following the Armistice he was attached to the Department of Sanitation of the Chief Surgeon's office in Tours.

Upon his return to the United States late in 1919, Colonel Ashburn was placed in charge of the Division of Venereal Diseases in the Surgeon General's Office. In 1920 he established the Medical Field Service School in

Carlisle, Pennsylvania, becoming its first Director, remaining in Carlisle until 1923 when he was detailed as Professor of Military Hygiene at West Point for a period of four years. In 1927 he was ordered to the Surgeon General's Office to become Chief of the Library Division and Librarian of the Army Medical Library. Colonel Ashburn was retired on account of disability in September, 1931, at the age of 59, but he continued on duty as Librarian until July 1, 1932, when he was relieved from active service. He was appointed Superintendent of Columbia Hospital for Women in Washington, D. C., in 1934, and remained in that position until a few months before his death on August 20, 1940.

He was a member of the American Medical Association and the Association of Military Surgeons, as well as being a Fellow both of the American College of Surgeons and the American College of Physicians.

Colonel Ashburn was recognized as an author of distinction and wrote a number of articles dealing with the work of the Medical Service of the Army. He was also author of two books, one the well-known *Military Hygiene*, and the other the important *History of the United States Army Medical Department*. He was made an officer of the French Legion of Honor in recognition of his distinguished service in the World War.

Colonel Ashburn was a widely known and highly esteemed officer of the Medical Corps. In a varied career in the Army covering more than a third of a century, he was an outstanding figure, and it may be said that he never filled a position without putting something of himself into it. As a student, as a physician, as a scientist, and as a figure in the educational world, he possessed wide culture and progressive knowledge. By nature he was quiet and undemonstrative, and anything approaching self-advertisement was repugnant to him. The writer of this brief tribute knew him well and saw him just as the blow had descended upon him—the knowledge that his death was a matter of but a few weeks. In that interview Percy Ashburn sought no comfort, no palliation of the sentence. He knew the truth and he faced it with singular fortitude and without complaint. He was a faithful servant whose work was well done, and he came to the end with courage and resignation. His friends will not forget him.

HAROLD W. JONES, M.D., Colonel, M.C., U. S. A.,
The Librarian, Army Medical Library

DR. LEON SHULMAN

Dr. Leon Shulman, F.A.C.P., Los Angeles, died at his home of coronary disease on September 14. Dr. Shulman was born in Paris, France, on April 7, 1885, but came to the United States as a child, lived and attended high school in Brooklyn, and came to California in 1905.

He received his medical degree from the University of California in 1911. He was a member of the faculty of the University of Southern

California School of Medicine from 1913 to 1919, and had been Associate Professor of Diseases of the Chest of the College of Medical Evangelists since 1919. Since 1912, he had been an Attending Physician, tuberculosis division, of the Los Angeles County Hospital. During the World War he was a member of the special board for tuberculosis at Camp Kearney, and at the time of his death was a Captain in the Medical Reserve Corps of the U. S. Army.

Dr. Shulman devoted his interest to diseases of the chest and was instrumental in the founding of the Sanitarium for Tuberculosis at Duarte, of which he was to become Consultant and Chief of Staff. He was a Diplomate of the American Board of Internal Medicine, a member of his county and state medical societies, the American Medical Association, the California State Tuberculosis and the National Tuberculosis Associations, the American Academy of Tuberculosis Physicians, the American College of Chest Physicians, and had been a Fellow of the American College of Physicians since 1923.

Dr. Shulman was an able and earnest worker and was highly respected by his fellow physicians. His active life was closed all too soon. He is survived by his widow, a daughter and a son, Dr. Leon Shulman, Jr.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Los Angeles, California

DR. EBEN CLAYTON HILL

Dr. Eben Clayton Hill, F.A.C.P., Baltimore, Maryland, and Temple, New Hampshire, died June 15, 1940, of coronary thrombosis, in the Burbank Hospital, Fitchburg, Massachusetts, at the age of 58 years.

Dr. Hill received his Bachelor of Arts degree in 1903 and his medical degree in 1907 from the Johns Hopkins University. Later he pursued postgraduate training in the Army Medical School and entered the Medical Corps of the Army, serving successively as First Lieutenant (1909–12) and Captain (1913), when he retired for disability in line of duty. Later in his career he was Assistant in Anatomy, Instructor in Anatomy and Associate in Anatomy at the Johns Hopkins Medical School, and served also for many years on the staff of the Vassar Hospital and Dispensary in Poughkeepsie, N. Y. In later years he had been Lecturer in Roentgenology at his Alma Mater.

He was a member of the Medical and Chirurgical Faculty of Maryland, the Baltimore City Medical Society, the American Association of Anatomists, the American Roentgenological Association, a Fellow of the American Medical Association and of the American Association for the Advancement of Science. He had been a Fellow of the American College of Physicians since 1916, and a Life Member since 1938.

DR. WILLIAM COLE

Dr. William Cole, F.A.C.P., Long Beach, California, died July 9, 1940, of coronary sclerosis, at the age of 48. He was born at Melita, Man., Canada, April 13, 1892. He graduated from the University of Manitoba Faculty of Medicine in 1913, and served during the World War in the Royal Canadian Army Medical Corps with the rank of Captain, with service in Canada, England, Belgium and France. He was a member of the Visiting Staff of the Long Beach Community, St. Mary's Long Beach and Seaside Memorial Hospitals.

Dr. Cole was a registrant of the General Medical Council of Great Britain, Diplomate of the American Board of Internal Medicine and a member of the Long Beach Academy of Medicine, Los Angeles County Medical Association, California Medical Association, American Medical Association, American Association for Study of Rheumatism, and had been a Fellow of the American College of Physicians since 1932.

DR. WILLIAM ALBERT EVANS

Dr. William Albert Evans, F.A.C.P., Detroit, Michigan, died June 9, 1940, of coronary occlusion, at the age of 63. He was born in Ontario, Canada, in 1876, and received his medical degree from the University of Michigan in 1902. He had served as Roentgenologist at the Harper, U. S. Marine and Manufacturers' Hospitals, and at one time was Associate Professor of Roentgenology at Wayne University College of Medicine. For several years he was President of the Detroit Board of Health.

Dr. Evans was a member of the Wayne County Medical Society, Michigan State Medical Society, Radiological Society of North America, the American College of Radiology, and a member of the Executive Council and a past President of the American Roentgen Ray Society. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1917.

DR. ZEBUD MacKAY FLINN

Dr. Zebud MacKay Flinn (Associate), Bayamon, P. R., passed away after a brief illness on August 3, 1940, at the Presbyterian Hospital in San Juan, P. R., at the untimely age of 41. In October, 1939, he arrived in Puerto Rico, working as resident physician at San Alberto Hospital in Bayamon until June, 1940, when he was asked to join the active campaign against tuberculosis conducted by the Health Department of the Island, being assigned for duty at the Ponce Hospital. Dr. Flinn arrived in Puerto Rico with an unusual background in the field of tuberculosis. He was the son of Dr. and Mrs. John W. Flinn, F.A.C.P., of Prescott, Ariz. Scion

of a distinguished and nationally known authority in the field of tuberculosis, his knowledge of this phase of internal medicine was thorough and deeply rooted.

Dr. Flinn was born in Kingman, Ariz., May 8, 1899, and came to Prescott with his parents in 1902. He received his preliminary education in the Prescott schools. In 1916, at the age of 17, he enlisted with the Canadian Air Force and saw active service in France. He served as an instructor in the Royal Air Force, and in 1918, as results of injuries received in air combat, was invalided home with the rank of first lieutenant. At the beginning of the present war his former chief in the Air Force, now a high ranking officer, offered him a captaincy in the Canadian Medical Corps, which Dr. Flinn declined. After the World War, Dr. Flinn studied medicine in Edinburgh, Vienna and in Halifax. He was graduated from Dalhousie University Faculty of Medicine with the M.D., C.M. degrees in 1932. Before coming to Puerto Rico he practiced medicine in Albuquerque, N. M., and in Prescott, Ariz., and for several years worked at the Pamsetgaaf Sanatorium, Prescott.

His various scientific contributions dealt with blood studies in pulmonary tuberculosis and with pulmonary bronchomoniliasis. During the past six months, and under the auspices of the Department of Health of Puerto Rico, he delivered lectures by radio on different aspects of the tuberculosis problem, and published a paper entitled, "Pulmonary Tuberculosis and Tropical Diseases" in the Puerto Rico Health Bulletin. At the time of his death, Dr. Flinn was an Associate of the American College of Physicians, having joined the College in 1936.

His was a charming and dynamic personality always ready to help his fellowman. By his passing, Puerto Rico loses a leader in the struggle against tuberculosis and his family, friends and associates have suffered an irreparable loss.

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